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Contents for January-February, 1959

COMPONENTS OF MILK AND THEIR SIGNIFICANCE TO THE ALLERGIC CHILD

Definitive diagnosis in the presence of milk-induced disturbances is important because of the differentiation of possible treatment. Newer techniques of protein fractionation provide a better understanding of ingested incitants, and offer a solution to some of the problems of dietary management. Vitamin A absorption is a major concern in allergic individuals, especially those on milk-free diets.

Joseph H. Fries, M. D., F.A.C.A., (Stanley J. Lagin Pediatric Research Laboratory, North Shore Hospital, Manhasset, N. Y.) New Hyde Park, New York 1

ALLERGIC FATIGUE AND TOXEMIA

Allergic fatigue and toxemia due to food allergy first reported in 1930 is again emphasized. Their occurrence from pollen allergy first reported by Kahn in 1927 and recently by Moore is also confirmed.

Albert H. Rowe, M.D., F.A.C.A., (Lecturer in Medicine, Emeritus, University of California Medical School, San Francisco, California), Oakland, California 9

THE CLINICAL EVALUATION OF PARABROMDYLAMINE MALEATE (DIMETANE®)

Results of treatment on allergic patients using parabromdylamine maleate (Dimetane®), a new antihistaminic agent, revealed this drug to be more efficient in our hands than all other drugs, particularly as to side reactions such as drowsiness.

William H. Lipman, M.D., F.A.C.A., (Lipman-Olsman Clinic), Kenosha, Wisconsin 19

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J. Warrick Thomas, M.D., F.A.C.A., (Assistant Clinical Professor of Medicine, Medical College of Virginia, and Director of The Thomas Clinic), Richmond, Virginia 25

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Maury D. Sanger, M.D., F.A.C.A. (Assistant Professor of Pediatric Allergy, Albert Einstein College of Medicine), Brooklyn, New York 173

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Bernard A. Berman, M.D., Brookline, Massachusetts, *George L. Engel, M.D.*, and *Jerome Glaser, M.D., F.A.C.A.* (Departments of Pediatrics and Psychiatry, University of Rochester School of Medicine and Dentistry and the Pediatric Services of the Strong Memorial-Rochester Municipal Hospitals), Rochester, New York 188

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A 50 per cent acetylcholine aerosol induced bronchial obstruction in subjects with asthma and resulted in a diminution of spirometric functions. Diphemanil methylsulphate, aminophylline, epinephrine and hydroxypropyl theophylline reversed this effect, in that order. Only epinephrine and diphemanil methylsulphate prevented it.

D. Edward Frank, M.D., F.A.C.A. (Assistant Clinical Professor of Medicine, University of Southern California), Los Angeles, California 200

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Otis Field Jillson, M.D. (Assistant Professor of Dermatology, Dartmouth Medical School), and *William L. Curwen, M.D.*, and *Bronson R. Alexander, M.D.* (Residents in Dermatology, Hitchcock Clinic), Hanover, New Hampshire 215

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Arthur Lipschutz, M.D. (Associate Professor of Pediatrics, Hahnemann Medical College and Hospital), Philadelphia, Pennsylvania..... 336

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M. Murray Peshkin, M.D., F.A.C.A. (Chief Medical Consultant, Jewish National Home for Asthmatic Children, Denver, Colorado), and *Harold A. Abramson, M.D., F.A.C.A.* (Consultant, Research Psychiatry, State Hospital, Central Islip, New York), New York, New York..... 344

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Rudolph S. Lackenbacher, M.D. (Attending Dermatologist at Columbus Hospital and Frank Cuneo Hospital), Chicago, Illinois..... 355

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Nathan Schaffer, M.D., F.A.C.A., F.A.A.A. (East Orange General Hospital), East Orange, New Jersey, *Norman Molomut, Ph.D.* (Waldeman Medical Research Foundation, Inc.), and *J. George Center, M.S.* (Center Laboratories), Port Washington, New York..... 380

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Bennett Kraft, M.D., F.A.C.A. (Attending Physician and Chief, Allergy Clinic, General Hospital), *Frank W. Countryman, M.D.* (Assistant Professor of Psychiatry, Indiana University School of Medicine), and *David L. Blumenthal, M.S.W.*, Indianapolis, Indiana 394

THE STUDY OF ALLERGIC REACTIONS IN THE ETIOLOGY OF BRONCHIECTASIS

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Stanley L. Goldman, M.D., F.A.C.A. (Kansas City General Hospital), Kansas City, Missouri 399

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E. G. Wygant, M.D. (Associate Fellow of American College of Allergists), Chicago Heights, Illinois 402

SOME THOUGHTS ON THE NATURE OF ALLERGY

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William B. Sherman, M.D. (Attending Physician, Roosevelt Hospital), New York, New York 407

EXHIBIT—MECHANICAL AIDS AND DRUGS. Bronchial Obstruction and Bronchospasm

Periods of hospitalization along with a variety of mechanical breathing apparatus, physiotherapeutic rehabilitation, antimicrobial and hormonal agents, and use of therapeutic aerosols and oxygen therapy make it possible to prolong life and restore many asthmatic patients to a life of economic usefulness.

Maurice S. Segal, M.D., F.A.C.A. (Clinical Professor of Medicine, Tufts University School of Medicine, and Director, Lung Station (Tufts) and Department of Inhalation Therapy, Boston City Hospital), *Ernst O. Attinger, M.D.* (Assistant Professor of Medicine, Assigned to Lung Station (Tufts) and Department of Inhalation Therapy, Boston City Hospital), and *Merrill M. Goldstein, M.D.* (Research Fellow, American Trudeau Society; Lung Station (Tufts), and Boston City Hospital), Boston, Massachusetts 413

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Constantine J. Falliers, M.D., M. Bekaroglu, M.D., and *M. Murray Peshkin, M.D., F.A.C.A.*, New York, New York 434

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Roy Patterson, M.D., Jose N. Correa, B.S., and *Kenneth P. Mathews, M.D.* (Department of Internal Medicine, University of Michigan Medical School), Ann Arbor, Michigan 444

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John T. McCarthy, M.D., and *Beatrice Maher Kesten, M.D.* (Department of Dermatology, College of Physicians and Surgeons, and Dermatology Service, Presbyterian Hospital), New York, New York..... 519

PULMONARY DENERVATION AND RESECTION IN ASTHMATIC PATIENTS

Intractable asthma may be perpetuated by structural abnormalities in bronchopulmonary segments which act as "trigger mechanisms." Surgical exploration permits direct inspection of the lung and testing of segments as to inflow and egress of air. Mechanical defects can be corrected forthwith and sympathetic, parasympathetic or both denervations carried out simultaneously. Long-term studies in forty-three cases of intractable asthma have shown varying degrees of betterment with substantial improvement in the health status of two-thirds of the patients.

Richard H. Overholt, M.D. (New England Deaconess Hospital, New England Baptist Hospital, and Overholt Thoracic Clinic), Boston, Massachusetts.... 534

AN EVALUATION OF TRIAMINIC® AND HYDROCORTISONE IN THE TREATMENT OF NASAL ALLERGY, NASAL POLYPOSIS, AND ASTHMA

Cases of chronic allergic rhinitis responded well to oral treatment with two antihistaminic agents and phenylpropanolamine. Adding small amounts of hydrocortisone to the regimen produced marked relief of nasal polyposis, but no change in the chronic asthma.

Walter R. MacLaren, M.D., F.A.C.A. (School of Medicine, University of Southern California, and Allergy Clinics Los Angeles County General Hospital), Pasadena, California..... 546

THE TREATMENT OF NASAL POLYPOSIS

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Walter E. Owen, M.D., F.A.C.A., Peoria, Illinois..... 557

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Sidney Dann, M.D., Frederick R. Brown, M.D., Imelda A. Bautista, Aaron D.

Spielman, M.D., F.A.C.A., and *Herbert S. Kupperman, M.D., Ph.D.* (Department of Therapeutics, New York University Bellevue Medical Center and Allergy Clinics of the Beekman-Downtown, Bellevue and Beth Israel Hospitals), New York, New York 562

PSEUDOALLERGIC SCHIZOPHRENIA

The concept of Hoch and Palatin concerning certain psychoneurotic patients who should be classified as pseudoneurotic forms of schizophrenia has been applied to a group of patients complaining of allergy symptomatology. Six case histories are reviewed and it is proposed that they be classified as pseudoallergic schizophrenia. The application of Hoch's concept to the diagnosis and treatment of this group of allergic patients has resulted in improved diagnostic and therapeutic possibilities.

Harold A. Abramson, M.D., F.A.C.A. (Biological Laboratory, Cold Spring Harbor, New York, and the Community Hospital, Glen Cove), New York, New York 576

SULFONAMIDE THERAPY IN THE PREVENTION OF ASTHMA ASSOCIATED WITH INFECTION

Asthma associated with infection not responsive to the customary antiallergic measures was controlled in a majority of seventy-one patients when sulfonamide drugs were administered prophylactically, with nausea in two patients the only adverse reaction. This allowed us to hold antibiotic agents in reserve for emergencies.

A. E. Fishman, M.D., F.A.C.A. (Chief of Allergy, St. Agnes Hospital) Philadelphia, Pennsylvania 588

THE EFFECT OF MIGRATION TO MIAMI, FLORIDA, ON ALLERGIC RESPIRATORY DISEASE

A substantial number of people with allergic respiratory disease will improve after migration to Miami, Florida, where hay fever is a rare manifestation of allergy.

George Gittelson, M.D. (Department of Medicine, School of Medicine, University of Miami, and the Jackson Memorial Hospital), Miami, Florida 596

A LONG-ACTING TRIPLE ANTIHISTAMINE

Tridecamine®, a long-acting triple antihistamine is the subject of this preliminary report. For the relief of allergic complaints, the results were found to be equal or superior to those resulting from other antihistaminic preparations. Few side-effects were observed.

Lawrence J. Halpin, M.D., F.A.C.A., Cedar Rapids, Iowa 602

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K. K. Chen, Ph.D., Madison, Wisconsin, and *Carl F. Schmidt, M.D.,* Philadelphia, Pennsylvania 605

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Jale Duvenci, M.D. (Fellow in Medicine), *Sanford Chodosh, M.D.* (American Trudeau Fellow in Medicine), and *Maurice S. Segal, M.D., F.A.C.A.* (Clinical Professor of Medicine, Tufts University School of Medicine), (all Lung Station, Tufts, Boston City Hospital), Boston, Massachusetts.. 695

TREATMENT OF SEVERE ALLERGIES WITH DEXAMETHASONE

A new synthetic adrenal steroid hormone, dexamethasone, (Deronil) provided marked relief of symptoms in nearly all of thirty-nine patients with asthma, allergic rhinitis, and/or allergic dermatoses. Side effects were mild, and no serious adverse reaction occurred in any patient.

Fred A. Parish, M.D., F.A.C.A., Brockton, Massachusetts..... 701

DEXAMETHASONE: (A NEW CORTICOSTEROID. ITS EFFECT IN ALLERGIC DISEASE)

Dexamethasone is one of the newest anti-inflammatory steroids found to effectively control allergic symptoms. Therapeutic doses are considerably less than other steroids. A similar range of steroid by-effects are observed at these doses.

Alex S. Friedlaender, M.D. (Chief, Allergy Division, Department of Medicine, Grace Hospital, Detroit) and *Sidney Friedlaender, M.D.* (Assistant Clinical Professor of Medicine, Wayne State University College of Medicine, Detroit), Detroit, Michigan 705

TREATMENT OF DERMATOLOGIC AND RESPIRATORY ALLERGY WITH DEXAMETHASONE

Deronil (dexamethasone), used as adjunctive therapy in 100 patients with respiratory and dermatologic allergies, provided excellent or good relief of symptoms without significant side effects.

Jack A. Rudolph, M.D., F.A.C.A. (Consultant in Internal Medicine and Allergy, VA Hospital, Coral Gables, Florida and Instructor in Medicine, Miami University), and *Burton M. Rudolph, M.D., F.A.C.A.* (Associate, Hialeah Hospital, Hialeah, Florida, and Member of Jackson Memorial Hospital Out-Patient Clinic Staff), Miami Shores, Florida 710

THE USE OF DEXAMETHASONE IN THE TREATMENT OF ALLERGIC DISORDERS

Dexamethasone was used in the treatment of eighty-three patients with allergic disease. Results were good with a low incidence of side effects.

Paul Chervinsky, M.D., F.A.C.A., New Bedford, Massachusetts 714

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Dexamethasone (Decadron) proved effective in ameliorating ragweed hay fever symptoms with an average daily dosage of 1.0 mgm. in a small series of patients who had inadequate specific hyposensitization. No side effects were noted with its short term usage.

Mayer A. Green, M.D., F.A.C.A. (Assistant Clinical Professor, Allergy Section of the Department of Dermatology, University of Pittsburgh School of Medicine), Pittsburgh, Pennsylvania 717

ALLERGIC REACTIONS DUE TO F D & C YELLOW NO. 5 TARTRAZINE, AN ANILINE DYE USED AS A COLORING AND IDENTIFYING AGENT IN VARIOUS STEROIDS

Stephen D. Lockey, M.D., F.A.C.A., Lancaster, Pennsylvania..... 719

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Merle W. Moore, M.D., F.A.C.A. (Department of Medicine, Division of Allergy, University of Oregon Medical School), Portland, Oregon, and *Charles E. Reed, M.D., A.A.C.A.,* Corvallis, Oregon..... 722

ELIXOPHYLLIN IN THE TREATMENT OF ACUTE AND CHRONIC ASTHMA: CLINICAL EVALUATION AND PULMONARY FUNCTION STUDIES

Theophylline given orally in a 20 per cent alcoholic elixir improves

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Walter R. MacLaren, M.D., F.A.C.A. (Department of Medicine, Southern California School of Medicine and Allergy Clinics of Los Angeles County General Hospital), Pasadena, California 729

THE USE OF TRIAMCINOLONE IN THE TREATMENT OF ALLERGIC DISORDERS
Triamcinolone, given in short courses of therapy to suppress active cutaneous or respiratory symptoms of hypersensitivity, effectively carried the allergic patient through severe and disabling situations. Side effects were minor at dosage levels employed and required no special consideration.
Sydney F. Smith, M.D., F.A.C.A. (Middlesex and St. Peter's Hospitals), New Brunswick, New Jersey 740

NUMMULAR ECZEMA WITH SPECIAL REFERENCE TO DERMATITIS OF THE HANDS IN HOUSEWIVES
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Paul Gross, M.D. (Department of Dermatology, Columbis-Presbyterian Medical Center), New York, New York..... 745

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Calcium potassium glutamates seem to be useful in the treatment of elderly asthmatic patients with complications. This drug, Capomate, primarily liquefies viscid bronchial secretions and subsequently, other anti-asthmatic measures prove to be more effective.
S. R. Zoss, M.D., F.A.C.A. (Chief of Allergy, Youngstown Hospital Association) Youngstown, Ohio 755

FURTHER OBSERVATIONS WITH ANTIHISTAMINES IN REDUCING REACTIONS IN INTRAVENOUS PYELOGRAPHY
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Maury D. Sanger, M.D., F.A.C.A. (Attending Allergist Veterans Administration, Brooklyn Out-patient Clinic), Brooklyn, New York..... 762

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Louvane A. Fox, M.D., F.A.C.A. (Keene Clinic) Keene, New Hampshire.. 768

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Bernard Dickstein, M.D., F.A.C.A., Flint, Michigan..... 784

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Carlos Tejo, M.D., Joaquin C. Bido, M.D., Simon Tomasini, M.D., and *Robert D. Barnard, M.D.* (Departments of Pathology and Surgical Research, Harlem Hospital, New York City Department of Hospitals), New York, New York 855

REHABILITATION OF CHILDREN WITH INTRACTABLE ASTHMA

W. B. Steen, M.D., F.A.C.A., Tucson, Arizona 864

ALLERGY AND RECURRENT EPISTAXIS IN CHILDREN

Donald H. Walker, M.D., F.A.C.A. (Department of Otolaryngology, Sharon General Hospital), Sharon, Pennsylvania 872

DURATION OF EFFECT OF A SUSTAINED RELEASE MIXTURE OF ANTIHISTAMINIC AGENTS: TRIDECAMINE

Tridecamine Dospan, a new sustained-release triple antihistaminic preparation, was evaluated on the basis of its duration of effect. The results of this study confirm the fact that Tridecamine is long-acting and maintains its effect over a twelve to fourteen-hour period.

T. L. Jones, M.D., L. B. Dale, Ph.D., and *G. L. Christenson, B.S.*, Cincinnati, Ohio 878

PRELIMINARY STUDY OF USE OF BUCCAL PROTEASE THERAPY IN BRONCHIAL ASTHMA

In older chronic bronchial asthmatic patients the infectious component can be better destroyed by the use of buccal proteases in conjunction with antibiotics and hyposensitization.

Donald B. Frankel, M.D., F.A.C.A., Abe B. Aaronson, M.D., F.A.C.A., and *Norman J. Ehrlich, M.D., F.A.C.A.*, Chicago, Illinois 883

DEXAMETHASONE IN CHILDHOOD ASTHMA

Dexamethasone was found effective in controlling symptoms in 21 intractable asthmatic children and 1 asthmatic child, who also suffered from rheumatic pericarditis, at the Jewish National Home for Asthmatic Children.

Constantine J. Falliers, M.D., and *Samuel C. Bukantz, M.D.,* (Jewish National Home for Asthmatic Children, and Children's Asthmatic Research Institute and Hospital), Denver, Colorado 887

DEXAMATHESONE IN DERMATOLOGIC THERAPY

Orally administered Dexamethasone is a potent anti-inflammatory drug when used in the treatment of some dermatologic disorders. It is also effective topically in treating second degree burns and certain skin lesions.

Perry A. Sperber, M.D., F.A.C.A. (Director of the Dermatology and Allergy Clinic, Halifax District Hospital), Daytona Beach, Florida..... 895

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COMPONENTS OF MILK AND THEIR SIGNIFICANCE TO THE ALLERGIC CHILD

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ALTHOUGH medicine has made tremendous strides in its basic understanding of immunology, comparatively little progress has been made in recent years in the practical aspects of allergy—its diagnosis and therapy. One of the avenues which offers itself as a fruitful source of progress is the more critical analysis of the causative or antigenic factors. Chief among these, of course, is food, a more critical chemical analysis of which offers an improved approach to the management of the patient with an allergic disorder. Foods have many components, some non-specific irritants and others potentially allergenic. With increased knowledge of the multiplicity of proteins in foods, we become aware that sensitivity may exist to one or to several of these components.

THE PROTEINS OF MILK

Milk, which is one of the most complex foods, offers the best possible example of the significance to allergy of the chemical breakdown of protein components. Milk should not be treated as one allergen, but as a complex of many allergens, and a patient may be sensitive to one or to several of these. Although we have been satisfied to date with its separation into three major protein fractions—lactalbumin, casein and lactoglobulin—and have paid relatively little attention even to these three, newer techniques of physical chemistry (electrophoresis, amino acid analysis, and ultracentrifugation) are offering us finer subdivisions into at least eight purer proteins.[1] (Table I).

From Stanley Jay Lagin Pediatric Research Laboratory, North Shore Hospital, Manhasset, New York.

Presented at the Fourteenth Annual Congress of The American College of Allergists, Atlantic City, New Jersey, on April 25, 1958.

TABLE I. PROTEINS OF MILK

*Lactalbumin (14% of total protein)	*Casein (82% of total protein)	*Lactoglobulin (2% of total protein)
Alpha-lactalbumin	$Alpha_1$-casein	Euglobulin
$Beta_1$-lactoglobulin	$Alpha_2$-casein	Pseudoglobulin
$Beta_2$-lactoglobulin	Beta-casein	Amylase
Serum albumin	Gamma-casein	
Peroxidase	Delta-casein	

MISCELLANEOUS PROTEINS

Fat Globule Surface Fraction (1% of total protein)	Proteose-Peptone Fraction (1% of total protein)
Lipoproteins	Two indistinct species
Xanthine oxidase	One electrophoretically
Alkaline phosphatase	distinct species

*These commonly known proteins—potentially allergenic—are not pure fractions. They have been subdivided by electrophoresis, ultracentrifugation, and newer immunologic and physiochemical techniques.

The albumin fraction constitutes 14 per cent of the total protein content of milk, and consists of at least five purer proteins, any or all of which may be potentially allergenic.

Casein (82 per cent of total protein), to which the possibility of sensitivity has been questioned by some,[2] also contains five subdivisions to date. When immunologic testing to these individual sub-proteins becomes practical, we may be able to establish their actual allergenicity.

The antigenicity of the immune globulins (2 per cent of total protein) in milk has never been studied. Even the fat globulins in milk have adsorbed on their surface lipo proteins and protein-containing enzymes, the antigenicity of which has never been explored. The same applies to the recently isolated proteose-peptone fractions.

Proteins have different physical and chemical characteristics which lend themselves to selective, individual denaturization so that the food itself may be modified to eliminate the offending allergenic protein and still make the nutrients available to the patient.[3]

Even in the presence of allergic sensitivity to milk, complete avoidance may not be necessary. Since, according to presently available information, most instances of allergic sensitivity to milk are due to the lactalbumin fraction, modification of the milk by boiling or evaporating may be adequate. On the other hand, if sensitivity exists to other protein fractions, it may be necessary not only to eliminate milk, but also the by-products of milk, as well as biologically related foods such as beef.

Figure 1 outlines a simple scheme for the substitution for regular milk where milk is a specific allergenic incitant. As mentioned above, boiling or heating incident to evaporation denatures the milk so that most milk-sensitive individuals will tolerate it. Since lactalbumin is a species-specific protein, substitution of other mammalian milks such as goat's milk is also practicable.

In contrast, casein is a heat-stable protein, common to all animal milks.

Sensitivity to this component implies sensitivity to all mammalian milks and suggests substitution with meat-base milks or the vegetable milks such as soybean preparations.

MILK PROTEINS AND MILK SUBSTITUTES

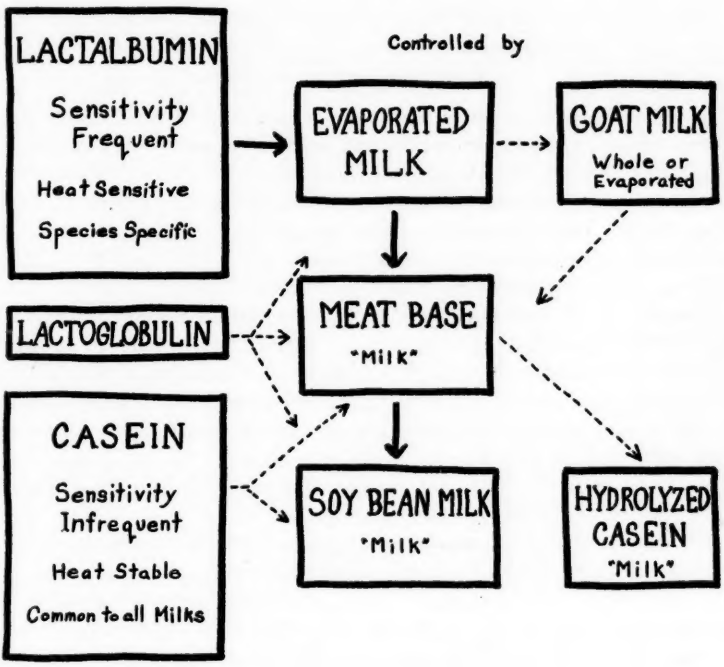

Fig. 1. Milk proteins and milk substitutes.

THE IMMUNOLOGIC RESPONSE

By strict interpretation, milk allergy is a specific immunologic, antigen-antibody response to milk. Milk allergy does not include all the abnormal reactions which may result from its ingestion. It is not enough to incriminate the incitant by the abatement of symptoms with the removal of milk from the diet, and the recurrence of the symptoms with its reinstatement.

There are generally accepted criteria for the diagnosis of allergy which have been unreasonably ignored in the diagnosis of milk allergy. These criteria, outlined in previous communications,[4] are based on unmistakeable

clinical expressions which are widely accepted as allergic in etiology. Among these are asthma, allergic rhinitis, urticaria, angioneurotic edema, atopic dermatitis, the rarer anaphylactic shock and, lastly, gastrointestinal symptoms when accompanied by any of the aforementioned.

These strict criteria are essential for medical documentation. However, for the practical practice of allergy, subsidiary evidence may have to be depended upon, such as confirmatory positive cutaneous tests, or a history of allergy among the immediate family or of the subject. In gastrointestinal symptomatology, roentgenographic confirmation may be possible.[5,6] It is helpful to find eosinophilia of nasal secretions or of blood.

THE NON-IMMUNOLOGIC RESPONSE

In the study of substances which cause abnormal manifestations, differences must be established between those which provoke reactions predicated on an immunologic basis, and those which provoke reactions initiated by non-immunologic mechanisms. Identical symptoms can result from both of these basic mechanisms. For the practical management of the patient with allergic disorders, a better understanding of these two widely different patho-physiologic categories is needed.

The problem of intolerance requires its own approach, implying, first of all, investigation of possible bacterial or other contamination,[7] a frequent factor when dealing with milk. With infants in particular, a scrutinizing of formula combinations and methods of preparation and feeding may be rewarding. Overfeeding and underfeeding, or too rapid or forced feeding should also be considered.

A serious concern which has recently presented itself is the chemical contamination of the cow's milk either via insecticides[8] or antibiotics in its food, or by therapeutic penicillin injections or antibiotic administration to the cow. Surveys of the Food and Drug Administration[9] report that up to 11 per cent of milk samples chosen at random contain penicillin in concentrations up to 0.55 units per milliliter. Also identified in trace amounts were other antibiotics such as bacitracin and tetracycline. One may assume that gastro-intestinal and even systemic reactions are probable in certain highly sensitive individuals.

Moreover, the possibility of sensitization of humans by repeated ingestion of even subtle trace amounts of penicillin is something to which serious consideration may have to be given. It may account for some of the inexplicable allergic reactions occurring after the first injection of this antibiotic.

There are a number of diseases induced by intrinsic factors in milk which are rare and therefore commonly overlooked. These illnesses, predicated on non-immunologic bases, present a wide variety of symptoms—gastro-intestinal, toxemic, and the like. Some of these could easily be termed allergy to milk.

In breast milk intoxication, Vitamin B deficiency in the mother pro-

duces toxic products in her milk which are capable of causing severe systemic illness in the child.[10,11] Large quantities of milk as prescribed in certain diets for ulcers interact with alkali and result in visceral disturbances which characterize the "milk-alkali" syndrome.[12] Prolonged feeding

TABLE II. INCIDENCE OF MILK ALLERGY—GENERAL POPULATION

Author	Incidence
1. Children:	
(a) Collins-Williams[24]	0.3%
(b) Cooke[35]	0.3%- 0.4%
(c) Rackemann[25]	1.0%
(d) Loveless[26]	1.5%
2. Infants:	
(a) Dees[39]	1.0%
(b) Clein[37]	6.6%
(c) Glaser[36]	7.0%
(d) Porter and Carter[30]	10.0%
3. Adults and children:	
(a) Vaughan[25]	1%- 1.5%
(b) Waldbott[25]	3%- 5.0%
(c) Rowe[31]	2%- 7.0%

TABLE III. INCIDENCE OF MILK ALLERGY—"ALLERGIC" GROUPS

Author	Sampling	Incidence
1. Milk sensitivity Based on cutaneous tests:		
(a) Peshkin[2]	Allergic children	10%
(b) Vaughan[25]	Food sensitive individuals	14%
(c) O'Keefe and Rackemann[2]	Eczematous children	25.6%
(d) Balyeat[3]	Atopic eczema	47%
2. Milk sensitivity Based on clinical symptoms:		
(a) Rowe[31]	Asthmatics	5.5%
(b) Eyermann[32]	Individuals with nasal symptoms	15%
(c) Rowe[31]	Food sensitive individuals	25%
(d) Dees[39]	Allergic infants	30.3%
(e) Davidson[33]	Allergic children over 6 years	40%
(f) Davidson[33]	Allergic children under 4 years	55%

of goat's milk may develop a macrocytic type of anemia reputedly related to the low content of Vitamin B_{12} in goat's milk.[13]

Galactosemia is a metabolic disturbance in humans wherein the galactose fraction of the milk sugar cannot be converted by the liver into glycogen.[14] This is probably due to a deficiency of the enzyme galactose-1-phosphate transferase, which allows galactose to accumulate until it becomes toxic, and produces systemic disease, including mental deficiency, damage to the liver, and formation of cataracts in the eye. Although milk may be avoided, minute quantities ingested in other foods, and lactose or galactose-containing substances not rigidly excluded from the diet may cause insidious damage.

Acceptance of a cause and effect relationship of symptoms with incitants (any symptoms with any incitants) without an attempt at diagnosis, may possibly result in failure to offer the patient adequate treatment. Control of overt symptoms by the elimination of milk may result in failure to

diagnose the disease, and hence failure to control its more dangerous aftermath. The control of apparent symptoms is not sufficient. Milk-induced diseases must be recognized.

INCIDENCE

These examples point out the fact that criteria for the diagnosis of milk allergy are not generally established, giving rise to a tremendous variation in incidence recorded in the medical literature. Tabulated incidence of milk allergy shows a variation of from 0.3 per cent to 55 per cent (Tables II and III). This variation is easily accounted for by the wide disagreement on what constitutes milk allergy. Symptoms vary from diaper dermatitis[15] (ammoniacal rash of the diaper area) to generally accepted allergic symptoms (anaphylactic shock, asthma, urticaria).

In addition, these figures show many of the fallacies of improper statistical sampling. Age groups are not comparable. Physicians reporting are of different specialties, which thereby affects the consistency of their sampling. There is no uniformity of methods of testing, intracutaneous tests being equated with the less sensitive scratch tests. Also, a variety of testing materials are used, some reporters testing with whole milk extract and others with lactalbumin alone.

Statistics on children with allergic disorders who have been under my direct observation would indicate an incidence by strict criteria of about 0.3 per cent of allergy to milk. However, some 5 per cent report having had symptoms referable to milk at some time in the past.[4]

VITAMIN SUPPLEMENTATION

There is documentation to show that Vitamin A is better absorbed when naturally dispersed in milk than when artificially supplemented in oily preparations.[16,17] Interest is mounting in the utilization in allergic children of Vitamin A and there is much evidence of the possibility of serious deprivation. Furthermore, there is some question as to whether the allergic gut may not be impaired for the proper absorption of vitamins. It is my opinion that in the gastrointestinal tract of allergic infants, especially those with gastrointestinal symptoms where there is impaired motor function, Vitamin A is less effectively absorbed.

My unpublished studies[18] on severely allergic children show poor Vitamin A absorption in some, as demonstrated by flat absorption curves. This phenomenon has also been described in the allergic celiac syndrome.[19]

Moreover, milk substitutes are themselves lacking in essential vitamins. The problem therefore bcomes more involved in the allergic infant maintained on a diet which omits mammalian milk. Here one must depend either on supplementation of vitamins during the manufacture of some of the milk substitutes, or on the integrity of the physician or parent in providing vitamin supplements.

In children maintained on milk-deprived diets, I have seen cutaneous

disturbances of the type attributable to Vitamin A deficiency (hyperkeratosis and extensive dryness of the skin) which improved with Vitamin A therapy. Bass,[20] among others,[21] has described keratomalacia—with instances of permanent blindness—and unusual cerebral responses[22] ascribed to Vitamin A deficiency in allergic children on synthetic milks without animal fats. Vitamin B deficiency with fatal outcome has been described in a child maintained on a milk substitute.[23]

Despite the popular use of vitamins, this problem is still current. Recently Wolf[34] reported eye damage resulting from Vitamin A deficiency in a child who was fed a milk substitute and for whom Vitamin A supplementation was inadequate.

Given the possibility of impaired absorption, plus the fallibility of supply of Vitamin A and other vitamins, it is probable that the allergic infant may actually need vitamins far in excess of usual requirements.

One cannot overemphasize the importance of vitamin supplementation in the diet of the allergic child, whether or not milk is retained as a food.

SUMMARY

1. Newer methods of food fractionation, particularly of milk, offer the possibility of modification of essential foods, making them available to the patient with allergic disorders.

2. Allergy to foods must be differentiated from non-immunologic intolerance to foods. To clarify this, a variety of food-induced diseases referable to milk are described.

3. The diagnosis of allergy should be confined to those symptoms which fulfill the generally accepted criteria for allergic disease.

4. Practical suggestions are made for substitution of milk in the diet of the allergic patient.

5. Analysis is made of reported incidence of milk allergy in the literature.

6. The importance of vitamin supplementation (with specific reference to Vitamin A) in the diet of allergic patients is emphasized.

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ALLERGIC FATIGUE AND TOXEMIA

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ALLERGIC FATIGUE and toxemia commonly occur in allergic patients. Irritability and restlessness have long been reported from anaphylactic shock in animals. Shannon, in 1922,[24] recorded nervousness, restlessness, irritability and crying in children and in a five-month-old baby, constant body movements and crying due to food allergy. Such symptoms may also occur with recurrent headaches and migraine which always need study of allergy as a possible cause. Varying degrees of these symptoms, moreover, may be associated with transient paralysis, paresis, paresthesia, delirium and even unconsciousness from allergy as reported in important articles by Foster Kennedy from 1926 to 1936.

Kahn,[1] in 1927, first reported pollen allergy as a cause. Recently Moore[3] has confirmed pollen allergy as a cause of fatigue and cerebral symptoms. He also referred to seasonal somnolence, reported by Steinberg, in 1942, and to epilepsy associated with seasonal allergic rhinitis, reported by Cohen and Janjigian in 1955.

In 1930,[12] I reported food allergy as a more common cause, re-emphasizing it in 1931,[13] 1937[14] and 1944.[15] In 1950,[16] I published statistics concerning seventy patients, predominantly females, with these symptoms. The onset was any time from ten to seventy years, the condition having lasted one to forty years with an average duration of 9.4 years. Fatigue occurred in 94 per cent of these patients, "not rested on arising" in 57 per cent, aching and soreness in skeletal muscles and joints in 47 per cent, logginess, listlessness and drowsiness in 37 per cent, irritability or nervous tension in 34 per cent, despondency in 30 per cent, difficulty in rememberance and concentration in 27 per cent, insomnia in 11 per cent, fever in 10 per cent, tachycardia in 10 per cent, and night sweats, chilling and "goose flesh" in 3 per cent. Gastrointestinal symptoms occurred in 63 per cent, nuchal tension, aching and pain in 50 per cent, nasal allergy in 39 per cent, hives in 16 per cent, eczema in 10 per cent, bronchial allergy, urogenital allergy and epilepsy in less than 5 per cent. On skin testing there were a few reactions to foods which rarely revealed or harmonized with the causative food allergies which were responsible in 93 per cent of the patients. It did reveal "slight" to "definite" pollen reactions in most of the seven patients due to such allergy. Seven illustrative histories of patients were summarized.

These symptoms and fever up to 104° F both in children and adults were illustrated in a boy two and one half years old with "headcolds,"

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listlessness, sleepiness at times for three days and physical inactivity. Subnormal mentality had been diagnosed. Normal energy and alertness resulted from elimination of allergenic foods. A girl, seven years old, had "sinus attacks" with fever up to 105° F every four to eight weeks. She was listless, refused to play, inefficient in school, and refused most foods. She stated, "I feel like a rag doll." A normal, active, happy, hungry child resulted from her eliminated diet.

This fatigue and toxemia has been confirmed by Alvarez and Henshaw in 1935, by Moreno, in 1940,[4] and 1943,[5,6] and by Mariante, in 1944.[2] T. G. Randolph, especially, has confirmed and greatly elucidated these manifestations of allergy. In 1945,[8] he stressed their frequent occurrence, usually attributed erroneously to psychosomatic causes or neurasthenia. In 1948,[9] and 1949,[11] he reported food allergy as one cause of torticollis or "wryneck" and especially of nuchal myalgia[10] resulting in stiffness and deep soreness in the neck, shoulders, and upper back muscles. Other symptoms of allergic toxemia occurred in varying combinations and degrees. In 1951,[11] Randolph again wrote an informative article on myalgia allergy especially in the posterior cervical and trapeius muscles. Less often soreness, pain and tautness occurred in pectoral, intercostal, abdominal, lumbar, ham string and calf muscles due to allergy, especially to foods. At times the generalized aching in muscles and joints I previously reported occurred. Pulling, drawing, tightness, aching and soreness especially in the cervical muscles had been designated as tension headaches, attributed to nerve tension and not to the causative allergies. Tender nodules were reported in the involved muscles in the neck or even in the calf or other skeletal muscles, with frequent muscular cramping. Randolph found house dust causative in some patients.

In the last eight years we have studied many additional patients with fatigue due to allergy, aching and soreness in muscles and joints, mental confusion, dopiness, inability to concentrate, irritability, depression and other less frequent symptoms of allergic toxemia. In all patients other possible causes have always been carefully considered and excluded. In many patients, some or many of these symptoms were usually associated with gastrointestinal or naso-bronchial manifestations of allergy also due to food or pollen allergy. Nasal allergy and allergic headaches have been frequent. Some patients have only one to three of the toxic symptoms such as aching in muscles and joints, fatigue and hives as in Case six in this article. Or fatigue, lack of energy and persistent mild temperature may occur with no other manifestations of allergy as in a girl ten years old,[21] who had been abed for eighteen months with restricted activity for four years. Sulfadiazine had been given for two years because of assumed rheumatic fever, with an initial cereal-free elimination diet, and later a milk, corn and wheat-free diet. She was free of fatigue and fever in three weeks, remaining so in the last year. Other similar patients with fever or fatigue have been relieved with the indicated elimination diets.

A man, fifty-four years old, had constant nasal blocking and pressure in the antra, persistent frontal headache exaggerated for two to three days each week for ten years. Moderate fatigue and mental confusion had occurred. With the cereal-free elimination diet he was relieved of all symptoms in two weeks. Milk and wheat are still being eliminated. Moreover, fatigue with varying toxic symptoms commonly results from uncontrolled pollenosis, as first reported by Kahn. They may be reactivated at times by excessive doses of pollen antigens.

To illustrate further and emphasize the occurrence of this fatigue and allergic toxemia, the following adult patient histories are summarized. Though the so-called collagen diseases are probable results of hypersensitivity, they were not included in my former statistics and are not considered in this article because of the unknown nature of the responsible allergy.

CASE REPORTS

Case 1.—A man, thirty-four years old, had constant fatigue for fifteen or more years. After ten to fourteen hours of sleep, confusion, dopiness, irritability, daydreaming, difficulty in thinking and concentration, a dull frontal headache continued. Generalized aching, especially in the back of the neck, shoulders and hip joints persisted. Driving against lights increased his headaches and irritability. During cold weather his symptoms had been increased, associated with a constant chilling of the body.

Post-nasal mucus, nasal congestion and burning and fullness in the epigastrium occurred most of the time.

Diet history only indicated eggs as one cause for headaches. Family history revealed toxicity and indigestion for forty years in the mother.

Results of the physical and comprehensive laboratory and x-ray studies and skin tests for allergy were negative except for a boggy nasal mucosa.

With our fruit-free elimination diet plus rice, there was improvement in six days. In one month it was greater. Soy products had caused distention. In two months, he was entirely comfortable. In five years his symptoms are absent with the continuing elimination of milk, wheat, fruits, flavors and condiments.

Case 2.—A nun, thirty years old had had fatigue, confusion, dopiness, depression, lack of energy and difficulty in concentration for ten years, that impaired her teaching ability. She was "half sick" all the time.

Perennial nasal allergy suggesting a "headcold" had persisted. It was exaggerated in May, being associated with itching of the eyes for two years. Eczema of the palms and dorsa of the hands had not responded to dermatologic therapy for eight years. Sciatic pain in the right leg had increased for seven years. Diet history revealed a life-long dislike for milk.

On skin testing there were two-plus reactions to grass and tree pollens. With the cereal-free elimination diet for the study of food allergy, all fatigue, mental symptoms, eczema of the hands and sciatic pain disappeared in one month. Pollen therapy in the spring was also given with relief of her hay fever in May.

For the last eight years, egg and milk have reproduced toxemia, nasal allergy and hand eczema.

Case 3.—A man, forty-eight years old had severe fatigue—unrelieved by a long sleep, allergic toxemia, headaches, nasal block and marked post-nasal discharge for

four years. Logginess, inability to concentrate or remember, excitability, depression, pain in his head with thinking had prevented work as a food checker for eight months. "Sometimes he feels as if he would lose his mind." All symptoms increased in the late fall and winter and also were exaggerated when he was near the ocean. Epigastric burning and distention had continued for three years.

He had long disliked milk; fruits increased epigastric distress.

A son had hay fever; his paternal grandmother had asthma.

The results of physical and laboratory examinations and skin testing with foods and inhalants were negative, except for edema of the nasal mucosa and post-nasal mucus and a one-plus reaction to house dust.

With the fruit and cereal-free elimination diet, all symptoms decreased in a week and were absent in three weeks. He resumed work being "able to think and face the day's work."

During the last three years, milk, wheat and other cereals have reproduced his cerebral symptoms and fatigue. Both cooked and uncooked fruits reproduced his epigastric burning.

Case 4.—A man, forty-five years old, had perennial fatigue, mental depression, confusion, dullness and difficulty in concentrating and remembering along with perennial nasal allergy and slight asthma for five years. "Things looked blue." Fatigue was especially marked in his arms. Stiffness and tension were constant in the back of his neck. Nasal congestion, frequent blocking and much post-nasal mucoid discharge had continued for five years. Injections of autogenous vaccines for eighteen months had been ineffectual. Burning and "fire" in his stomach and under his sternum had persisted for several years, exaggerated by onions and honey.

A son had asthma controlled by my elimination diet.

Physical examination, x-ray of his lungs and sinuses, routine laboratory studies and skin testing with foods and inhalants were negative except for three-plus reactions to timothy and redtop which grew in his area.

To study food allergy, my fruit and cereal-free elimination diet was ordered. Fruits were also excluded because of his sub-sternal epigastric burning which in our experience is often due to allergy to fruit. Relief from fatigue and cerebral symptoms was delayed for two weeks becoming assured, however, in six weeks. Relief has continued for five years, necessitating the elimination of milk, fruits, coffee, and uncooked vegetables. The uncooked vegetables and fruits reproduced his epigastric and substernal burning.

Pollen therapy was given for a limited period because of large reactions. In the last four years, symptoms have been controlled by diet alone, indicating that his pollen reactions were not associated with clinical allergy.

Case 5.—A woman, thirty-five years old, had increasing fatigue, weakness, confusion, indecision, apprehension, depression, impaired memory, and emotional instability for five years. Weakness finally necessitated aid in walking. Sleep was restless and disturbed by dreams, especially of falling.

Hives and swellings, especially of the face, lips, feet and hands had recurred for five years. Headaches with nausea and frequent soreness and frequent vomiting had been recurring since adolescence. Pain and soreness in the lower abdomen, elbows, shoulders and knees had been helped by the elimination of tomatoes and fruits. Milk and egg had increased the localized swellings. Penicillin and sulfonamide drugs had caused edema and nausea. Belladonna had exaggerated most of her symptoms and caused "stiffness of the tongue."

The patient's father had probable bronchial and gastrointestinal allergy.

The results of physical examination, comprehensive laboratory tests, including skin tests with foods and inhalants were negative.

Previous diet trial had revealed various foods which had increased her symptoms. This history aided in formulating an initial minimal diet containing tapioca, white and sweet potato, chicken, turkey, salt and water along with multiple synthetic vitamins and calcium carbonate, one-half teaspoonful in water daily.

For the last five years all symptoms have been controlled using the above diet with the addition of rice, oats and lamb, one to two times a week; squab and duck also have been tolerated. Milk, egg, beef, pork, all fruits, condiments and spices reproduced symptoms. Rotation of various cooked vegetables in the diet has been tolerated at times.

In 1953, all symptoms recurred after inhalation of acacia pollen. Allergy to other tree and grass pollens was suspected. Desensitization to these pollens continued for over a year with apparent additional benefit. No such treatment has been given for the last four years.

Case 6.—A woman, forty-two years old, had had pain between the shoulders, in the hands, wrists, and elbows and left hip for twenty years. Increased severity had necessitated discontinuance of work as a waitress for the last six years. Frequent, and at times, prolonged bed rest had been ineffectual. Because of intermittent fever and suspicious teeth, total extractions had been done five years previously, but with no benefit. Increasing pain in the lower back had indicated a surgical corset for several months but with no help.

Along with this pain and soreness, fatigue had been constantly present. Sick headaches had occurred all of her life occurring three or four times during each recent year. Hives had been present all of her life at varying intervals.

Diet history revealed no dislikes or disagreements for any foods. The mother had had headaches; the maternal grandmother had asthma; the maternal grandfather had vomiting from morphine and hives from barbiturates.

On physical examination there were revealed pain and soreness with motion in various joints. On skin testing with important foods and inhalants the results were negative.

With the fruit and cereal-free elimination diet the pains had disappeared in ten days. In three months she had no distress or discomfort even while doing work in the house and garden. "I didn't think I would ever be free of pain and discomfort." During the last eight years this relief has continued, necessitating the eliminations of fruits, fish and condiments. She has been able to take small amounts of wheat, milk, and eggs, intermittently.

Case 7.—A woman, twenty-five years old, had had aching, soreness and edema in the arms spreading to the shoulders, neck, and upper back and lateral chest with mild and occasional aching and soreness in the thighs for fifteen months. This had prevented the use and the raising of her arms. Symptoms had been perennial in occurrence, exaggerted, however, in the spring, summer and fall. For two months in the summer she also had soreness and pain in the right eye, especially with upward vision. She also had pain under the sternum with swallowing. With these symptoms she had felt weak, dull, stupid, groggy, nervous, and dizzy. Prednisone, 10 mgs. daily, had ameliorated the symptoms. For many years she had had post-nasal mucus with morning hacking and coughing. Her diet and environmental histories suggested no allergy. Morphine and codeine had caused vomiting and headaches.

Physical examination, comprehensive laboratory studies, x-ray studies of the lungs and upper gastro-intestinal tract were non-contributory.

On skin testing there were slight reactions to several grass, fall and tree pollens and a one-plus reaction to cow's and goat's milk.

Because of exaggerated symptoms during the pollen seasons, desensitization with

a multiple all-season antigen was started, initiated with a 1:5 million dilution. It was gradually increased through the winter up to the 1:50 dilution which was well tolerated with good results. In two months, nearly or complete relief had developed. Increasing relief had continued during the last fifteen months. A temporary recurrence arose when 0.4 cc of the 1.50 dilution was administered. This was relieved by temporary reduction to the 1:500 dilution. Since then, 0.6 cc of the 1.50 dilution has been gradually attained and tolerated with no symptoms. In March, 1957 and 1958, hyacinths in the house caused a recurrence of all symptoms with gradual relief in one week after their removal.

Food allergy was studied with our fruit-free elimination diet with no resultant incriminations of foods except for exaggeration of nasal allergy from milk and abdominal cramping from pineapple. Meticorten® therapy was stopped in two months, but given for brief intervals when symptoms were activated by the hyacinths and temporary excess in pollen dosage.

COMMENT

Fatigue is the most common symptom of this syndrome due to allergy. It often persists on awakening even after a sleep, or rest for ten to twelve hours. A lack of energy and especially of initiative and enthusiasm occurs. It became so marked in Case 5 that walking required support. In addition to moderate and severe fatigue it occurs in a mild degree in many patients with other manifestations of allergy, not only due to food but also to pollens and drugs. Thus fatigue is not an uncommon symptom during hay fever due to pollen. Whether this is due to a generalized allergic reaction throughout the body or mainly in the skeletal muscles is unknown.

Mental symptoms including drowsiness, logginess, disability in concentration, thinking and memory, confusion, depression and irritability, emotional instability and nervous tension in varying combinations and degrees are best explained by cerebral allergy due possibly to edema or other results of vascular or other tissue reactivity. Along with irritability, disturbed sleep from annoying dreams may occur as in Case 6. A successful active lumbermill operator, Case 4, complained of depression and "feeling blue" along with his generalized fatigue. These symptoms reached a maximum degree in the remarkable Case 3, making thinking painful and nearly impossible which necessitated giving up his work as a food checker for eight months. Chilling with or without goose flesh may also occur in these patients as in Case 1. These mental symptoms were especially severe in Cases 1, 2, 5 and 7.

Headache was dull and constant for years in Cases 1 and 7. A constant, dull, frontal headache occurred in Case 3. Sick headaches for many years occurred every one or two weeks, decreasing gradually three to four times a year in Case 6.

Nuchal soreness, stiffness and pain are designated as headaches by many patients. This distress in the back of the neck may extend into the cervical and shoulder muscles and in the arms as in Case 4. It prevented raising the arms in Case 7. Most patients have had neck traction often

in hospitals with no help. Because of its great severity all teeth were removed, probably needlessly, in Case 6. Being a waitress, pain was also attributed to carrying trays and this occupation was discontinued. We have observed this nuchal allergy in mild degrees in many other patients, usually associated with various manifestations of allergy.

Pain, soreness and stiffness may occur in other skeletal muscles. The relief from the persistent sciatica in Case 2 may have resulted from the elimination diet which also relieved her of fatigue and cerebral symptoms. In Case 7 the aching, soreness and mild edema in the arms, spreading to the shoulders, neck, upper back and thighs for fifteen months and even the pain in the right eye with upward vision were relieved with desensitization to the pollens present in her area without any consideration of food allergy.

Perennial nasal allergy occurred in Case 1, suggesting a continuous cold in Case 2, causing marked congestion and blocking of the nose in Case 4. Postnasal mucus caused a hacking and clearing of mucus from the pharynx and a soreness of the throat in Case 7. Frequent occurrence of nasal allergy with the cerebral symptoms indicates a regional area of allergic reactivity in these adjoining affected tissues. Asthma occurs less frequently than nasal allergy.

Epigastric burning and distention occurred in Case 1, being associated with sub-sternal distress in Case 7. Burning distress was designated as "fire" in the epigastrium in Case 4. In our former statistics on seventy patients, these symptoms, with others in the gastrointestinal tract were the major manifestations in the allergic epigastric syndrome[18] we have previously reported.

Hives had recurred all through life in Case 6 and were associated with subcutaneous edemas in Case 5. Foods, and in the latter case, penicillin and sulfonamide drugs were responsible. Eczema on the dorsal and palmar surfaces of the hands[19,20] and on the fingers being present for eight years was entirely relieved, as I have formerly reported, along with the fatigue and toxic symptoms with the elimination of egg and milk in Case 2.

Other manifestations of allergy reported in our former series[16] of seventy patients were absent in these seven cases.

Diet histories in these seven cases gave little information indicating the responsible food allergies. None of the foods responsible for the symptoms in Case 1 was so revealed. The life-long dislike for milk in Cases 2 and 3 is not an uncommon history of clinical allergy to this food. However, the diet history as usual failed to show all the foods causing the symptoms in these patients.

Drug allergy was present in Case 5. In Case 7, morphine and codeine caused vomiting and headaches. In Case 6, a history of vomiting from morphine and of hives from barbiturates was elicited in the maternal grandfather. In no one of the seven cases did the fatigue and allergic toxemia arise from drug allergy.

The family history revealed probable allergic toxemia and gastrointestinal symptoms in the mother of Case 1. The maternal grandfather in Case 6 had hives from barbiturates. The son of the patient in Case 4 had the classical history of recurrent bronchial asthma[22,23] due to food allergy recurring from October to March and relieved by my cereal-free elimination diet. There was probable bronchial and gastrointestinal allergy in the father of Case 5, recurrent headaches in the mother of Case 6. This evidence of predisposition to various manifestations of clinical allergy was elicited in the family histories. Symptoms identical with those of the patients themselves were uncommon.

DIAGNOSIS AND CONTROL

Before or while allergy is being studied as a cause of fatigue and these various toxic symptoms, new growths, infectant, metabolic, endocrine, cardiovascular, genitourinary, and other less common causes must be carefully studied and excluded. It is to be stressed, moreover, that allergy must be ruled out by adequate and especially by its experienced study and treatment before psychosomatic causes are ever incriminated.

To study possible food allergy, trial diet with my elimination diets has[15,17] been utilized for thirty years. The test negative-diet rarely yields any relief. Usually my cereal-free elimination diet has been prescribed. Foods in the diet suspected of possible allergy or those giving large scratch reactions may be excluded. If legumes or other foods disagree, they are eliminated. The time required to obtain relief and the method of manipulation of the diet to obtain the desired results have been detailed in other publications.

Relief may be evident in four to fourteen days, increasing in the following weeks. Thus, in Case 1, it occurred in six days, being increasingly evident in the next three weeks and complete in two months. Improvement was apparent in one to two weeks in Cases 2 and 3, being complete in one month. In Case 4, relief was delayed for two weeks, gradually becoming assured in two months. In Case 5, some relief arose in ten to twelve days, but convincing benefit was delayed for two and one half months. The present diet listed below has maintained relief for five years. Definite relief from pains and fatigue arose in ten days in Case 6. In three months all distress was absent; energy and strength had returned. Finally, in Case 7, aching, soreness and limitation of motion in the neck, shoulders and arms and fatigue were absent or only slightly recurrent in two months, resulting from pollen therapy alone. This has continued with brief recurrences for fifteen months with such continued pollen desensitization.

The final elimination diets which have been necessary for the continued relief of symptoms in six cases follow:

In Case 1, milk, wheat, fruit, flavors and condiments have been excluded for five years. As in all cases, multiple vitamins have been given.

Egg, milk and its products, even in small amounts, have reproduced symptoms in Case 2 during the last eight years.

The incapacitating mental symptoms, nasal allergy and fatigue have been absent with the elimination of milk, wheat, and cereals for three years in Case 3. The patient's epigastric allergy has also required the exclusion of all fruits and uncooked vegetables.

In Case 5, milk, egg, beef, pork, wheat, fruit, spices and condiments have been necessarily eliminated for five years. Rotation of several vegetables and at times of beef and wheat has allowed their ingestion with minimum difficulty.

In Case 6, the elimination of fruit, fish, condiments and the occasional rotation of milk and egg in limited amounts in the diet, has been required for relief during the last eight years.

As noted above, the aching, pains and fatigue in Case 7 have been controlled for eighteen months with desensitization to pollens.

SUMMARY

The common occurrence of fatigue and allergic toxemia in children and adults arising from food and less often from pollen allergy, has received increasing corroboration.

Fatigue occurs in mild to severe degrees. This fatigue and toxemia may be so marked that physical and mental incapacitation may prevent actual work and efficiency in occupation, business or home.

Allergic toxemia usually accompanies the fatigue. Logginess, listlessness, drowsiness, aching and soreness in skeletal muscles and joints, especially in the cervical, shoulder, and arm regions and less so in other muscles, irritability, tension, depression, insomnia, difficulty in concentration and thinking, and fever may occur.

Gastrointestinal and nasal allergy and less often hives, eczema, and urogenital symptoms may be accompanying allergic manifestations.

Nuchal and other muscular allergies, associated with fatigue and varying numbers and degrees of the above symptoms may be distressing and invaliding as emphasized by Randolph.

This fatigue and toxemia were evidenced in seven illustrative cases. Confusion, dopiness, inability to think, fatigue and other symptoms forced resignation from his job in Case 3. Previous studies and treatment even by "thirty physicians" in Case 6 failed to give relief in all these cases.

With the accurate use of elimination diets, relief was evidenced in one to two weeks, being complete in one to two months in the first six cases. The final diets necessary for freedom from symptoms are detailed. Pollen desensitization alone relieved the symptoms in Case 7.

Allergy, along with all other possible causes of fatigue and toxemia, must be excluded before a diagnosis of psychoneurosis is justified.

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FOR FUTURE GENERATIONS

"I do not think at all that I am able to present here any procedure of investigation that was not perceived long ago by all men of talent; and I do not promise at all that you can find here anything quite new of this kind. But I shall take pains to state in clear words the rules and ways of investigation which are followed by all able men, who in most cases are not even conscious of following them. Although I am free from the illusion that I shall fully succeed even in doing this, I still hope that the little that is presented here may please some people and have some application afterwards."—BERNARD BOLZANO, *(1781-1848)*

THE CLINICAL EVALUATION OF PARABROMDYLAMINE MALEATE (DIMETANE®)

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THE purpose of this study is twofold: (1) To report our results of treatment on a number of patients ranging from five months to seventy-eight years of age and using Dimetane® (parabromdylamine maleate) in its various dosages. (2) To compare our results of treatment with a similarly treated control group of patients, ranging from six months to seventy-five years of age, using the antihistaminic drug, Chlor-Trimeton® Maleate (chlorprophenpyridamine).

METHODS AND MATERIAL

During the past ten months prior to the initiation of our clinical studies on patients treated with the new antihistamine drug, parabromdylamine maleate (Dimetane®), we had carefully observed a selected group of eighty-six patients who had been treated with chlorprophenpyridamine (Chlor-Trimeton® Maleate). These patients had been divided into two groups: (a) one group of patients with mild to moderate allergy syndrome complexes such as simple hay fever rhinitis, perennial rhinitis, et cetera, and a group of allergic patients with a complicated syndrome complex, that is, those patients with more severe allergy syndromes of various combinations such as allergic rhinitis plus atopic dermatitis, or allergic rhinitis plus asthma, or atopic dermatitis plus other complications. The above group we used as a control series.

In our studies with Dimetane,® we selected a group of ninety-three patients who were seen in our office and in the Kenosha Hospital. We attempted to match these as nearly as possible with the control group as to age, sex, similarity of symptoms, dosage of drugs, and length of treatment. These patients were likewise divided into the primary non-complicated allergic group and the complicated allergic group and these patients were studied over a ten-month period. While absolute patient-for-patient comparison would be difficult if not impossible because of the obvious variables, the over-all relative comparison of the groups was, in our opinion, fairly reasonable.

For the most part, our studies were concentrated mainly on the "primary" allergic disability groups since such groups would best lend themselves to clinical evaluation. However, we also recorded our findings in the so-called "complicated" allergy group since we were able to treat the latter group with both the antihistaminic agents (Dimetane® or Chlor-Trimeton®) plus steroid hormones.

Dimetane® supplied by A. H. Robins Co., Inc., Richmond, Virginia.

TABLE I. DIMETANE®-TREATED GROUP—UNCOMPLICATED ALLERGIES

Allergic Disturbance	No. of Patients	Clinical Response to Prescription			Side-Effects					
		Good	Fair	Poor	Drowsiness	Headache	Vertigo	Nervousness	Rash	Nausea
Fall hay fever rhinitis	18	14	4	0				1	1	
Spring pollen, grass, trees, molds	6	5	1				1			
Perennial rhinitis	24	16	5	3	2	1				
Acute urticaria and/or angio-edema	9	6	2	1						1
Chronic recurrent urticaria	6	3	2	1	1					
Atopic eczema (moderate, acute, subacute)	5	2	1	2						
Totals	68	46	15	7	3	1	1	1	1	1

TABLE II. CHLOR-TRIMETON®-TREATED GROUP—UNCOMPLICATED ALLERGIES

Allergic Disturbance	No. of Patients	Clinical Response to Prescription			Side-Effects					
		Good	Fair	Poor	Drowsiness	Headache	Nausea	Vertigo	Rash	Weakness
Fall hay fever rhinitis	22	17	4	1	6	2	1	2		1
Spring pollen, grass, trees, molds	6	4	1	1	3			1		
Perennial rhinitis	14	10	4	0	7	1			1	1
Acute urticaria and angio-edema	5	3	1	1	2	1	1			
Chronic recurrent urticaria	4	2	2	0	2			1		
Atopic eczema (moderate, acute, subacute)	3	1	1	1	1			1		
Totals	54	37	13	4	21	4	2	5	1	2

Hospitalized patients were seen daily and ambulatory patients were seen once to twice weekly the first two weeks and then once weekly up to eight weeks. Three forms of Dimetane® were employed in our clinical series, namely, the 12 mg Extentabs, given at twelve-hour intervals to all adult ambulatory patients, the 4 mg compressed tablets, at four-hour intervals to adult hospital patients, and at five-hour to six-hour intervals to children six to twelve years of age, and the Dimetane® Elixir to infants up to six years of age in various dosages. Likewise, in the control group, the 12 mg Chlor-Trimeton Repetabs® as well as the 4 mg compressed tablet and the Chlor-Trimeton® Elixir had been administered in a manner similar to that in which the Dimetane® was employed.

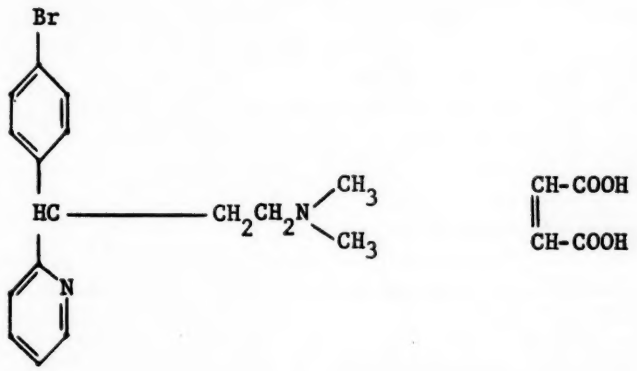
RESULTS OF TREATMENT

The results of our treatment are tabulated in Tables I, II, III and IV.

DISCUSSION

There are presently over a hundred antihistaminic agents now in clinical use and, for the most part, the majority of them have proved effective in relative degrees of efficiency. In our clinic, we have had occasion to give at least thirty-five of these preparations careful clinical trials at various times in over two thousand patients during the past nine years in a search

for a drug with the greatest antihistaminic effect and the least side-effects. In our clinical studies thus far, the two most effective compounds to date have proved to be (1) Dimetane® (parabromdylamine) and (2) Chlor-Trimeton® (chlorprophenpyridamine). In our opinion, both of these drugs have shown a relatively greater potency and safety factor on a weight basis, both in animal and human experimental studies, than have the other antihistaminic agents. Dimetane® is the most recently synthesized of the two antihistaminic agents. To date, it has proved the most effective and satisfactory in our hands; mainly, because of the absence of drowsiness and vertigo. Previous studies of Dimetane® obtained from the "Unpublished data supplied by the A. H. Robins Company, Inc." contains the essential pharmacology and some of the original clinical studies on Dimetane.® The brand name of this product is parabromdylamine maleate, and the chemical name 1-(p-bromophenyl)-(2-pyridyl)-3-dimethylamino-propane maleate. The structural formula is the following:



The above formula of Dimetane® is identical to that of Chlor-Trimeton® except for the bromine and chlorine, respectively. In Germany, Dimetane® is marketed under the trade name of Ilvin by Merck. In appearance, parabromdylamine maleate is a fine white crystalline powder, soluble in five parts of water, with a melting range of 130-135° C. The pharmacologic properties of Dimetane®, its *in vitro* antispasmodic activities, and its antihistaminic experimental studies with guinea pigs, mice, dogs, and monkeys, and the studies on chronic toxicity in monkeys were determined by Pharmacology Research, Inc.[1] All of the above were included in a special report of the A. H. Robins Co., Incorporated.[2] Essentially, these studies reveal: (1) Dimetane® to be equal to Chlor-Trimeton® as a histamine antagonist, (2) Dimetane® to be as low in toxicity as Chlor-Trimeton®, (3) Dimetane® to have the same therapeutic ratio as Chlor-Trimeton®. Blood studies as well as liver and kidney function tests, urine analysis, and autopsy findings reveal a high level of tolerance and safety.

TABLE III. DIMETANE® PLUS STEROID AGENT-TREATED GROUP—COMPLICATED ALLERGIES

Disease	No. of Patients	Clinical Response			Side-Effects					
		Good	Fair	Poor	Drowsiness	Vertigo	Weakness	Nausea	Nervousness	Edema
Contact dermatitis	10	6	2	2	2		2		2	
Allergic rhinitis, bronchitis, asthma, and atopic eczema	5	3	1	1						
Allergic rhinitis, bronchial asthma, and chronic urticaria	3	1		2						
Acute contact and subacute dermatitis and secondary fungus dermatitis	7	6	1		1	1	1	1*		
Totals	25	16	4	5	3	1	3	1	2	

*All side-effects in same patient.

TABLE IV. CHLOR-TRIMETON® PLUS STEROID AGENT-TREATED GROUP—COMPLICATED ALLERGIES

Disease	No. of Patients	Clinical Response			Side-Effects						
		Good	Fair	Poor	Drowsiness	Vertigo	Weakness	Nausea	Nervousness	Edema	Rash
Contact dermatitis	7	4	2	1	4		1			1	
Allergic rhinitis, asthma, and atopic eczema	9	6	1	2	5	1			1		1
Allergic rhinitis, asthma, and chronic urticaria	7	4	1	2	3		2	1			
Acute and subacute contact dermatitis plus fungus infection	9	5	3	1	6	2	1		1		
Totals	32	19	7	6	18	3	4	1	2	1	1

Clinical reports as yet unpublished to date by fifty-seven investigators[3] in the U. S. on 969 allergic patients treated with Dimetane® tablets and Dimetane® Extentabs reveal that the results were excellent or good in 790 patients, or 81.6 per cent, fair in ninety-three, or 9.8 per cent, with no response in eighty-six, or 8.6 per cent. Side-effects in these 969 patients totaled ninety-eight (10.15 per cent) with about eighty-two having drowsiness and vertigo. It was rarely necessary to discontinue Dimetane® because of these side-effects. Dr. H. A. Horstman, Jr.[4] from the Allergy Clinic of Georegtown University, reported a group of sixty-eight patients treated with Dimetane® with excellent results in fifty patients, moderate in ten, and negligible in eight. Side-effects in his series were slight in four patients and moderate in one.

Von Hansgeorg Weyer[5] reported a series of 262 allergic patients treated with oral and parenteral Ilvin, which is the same formula as Dimetane.® He found the antihistaminic effects good and the drowsiness infrequent (7 per cent).

R. Wawersig[6] treated 100 patients with Dimetane.® The itching in these

patients was previously unrelieved by the usual dermatologic therapy. In 45 per cent of his patients, there was "almost complete improvement," in 35 per cent "distinct improvement," and "no effect" in 20 per cent. There were no undesirable side-effects.

C. Shirren and K. H. Schulz[7] reported on the clinical and experimental investigations with this antihistaminic agent. Out of 100 patients treated, the results were good in seventy-eight, average in sixteen, and poor in seven. Best results were in patients with urticaria, angio-edema, and hay fever. Their best results were in the acute allergic skin and mucous membrane disorders and they stated "that patients with chronic disorders of the skin responded only slightly or not at all." The authors also commented "that the sedative effect which appears to be attached to many antihistaminic agents appears to be lacking in this particular antihistaminic agent."

J. Warrick Thomas[9] recently reported a clinical evaluation of Dimetane in 140 cases. Of this series, 129 patients tolerated the drug and eleven patients did not; 122 patients showed a satisfactory response to the drug. Only eleven patients of his series suffered side reactions—six of drowsiness, but five of his group could not tolerate any antihistamine. He concluded, "The response to treatment is favorable and, in certain instances, patients who were not able to tolerate other antihistamines tolerated Dimetane and obtained a satisfactory response."

It has, of course, been observed and shown by Gay, *et al*[8] in 1947 and 1948, and later confirmed many times by others, that the response to antihistaminic medications, as well as the response to drugs generally, varies from patient to patient, and thus, it is difficult to evaluate the effectiveness of drugs in disturbances due to allergies. However, our clinical observations were carried out on two groups of our own private patients whom we had observed and treated for months to years (even before the present studies) and to whom we had at various intervals during the past months and years given a variety of other antihistaminic medications, either in conjunction with our allergic management, or incident to such management. We were intimately acquainted with the previous histories, family backgrounds, and personal habits of these patients. We are, therefore, not cautious in stating that our observations of these patients are a relatively fair basis for our conclusions.

SUMMARY

Two groups of patients were studied over equal ten-month periods using the new antihistaminic agent Dimetane®, as a clinical study group, and the antihistaminic agent Chlor-Trimeton®, as a control group. Each group was divided into a primary mild and complicated allergy group and the results of treatment in both groups were carefully observed. Both drugs proved to be equally efficient but the incidence of side-reactions in

the Dimetane®-treated group proved to be the lowest by a considerable margin. These patients had previously been under management for allergy only.

CONCLUSIONS

1. Dimetane® (parabromdylamine) and Chlor-Trimeton® (chlorprophenpyridamine) are equally effective in the treatment of primary allergic syndromes.
2. Dimetane® and Chlor-Trimeton®, plus the steroid hormones, were equally effective in the treatment of complicated syndromes due to allergies.
3. Dimetane® (parabromdylamine), in our series, gave the lowest incidence of side-reactions, particularly drowsiness and vertigo.
4. In our hands, Dimetane® (parabromdylamine) has proved to be the safest antihistaminic agent that we have used in the treatment of disturbances due to allergies.

ADDENDUM

Since the preparation of this paper, we have treated an additional 145 patients on Dimetane, and of the total 238 patients treated with Dimetane, results are gauged as good 68 per cent, fair 22 per cent, poor 10 per cent, with side effects of drowsiness 6.7 per cent, total side effects 15.5 per cent.

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Submitted April, 1958

THE TREATMENT OF MAJOR ALLERGIC MANIFESTATIONS WITH DIMETANE INJECTABLE®

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WE are keenly interested in new therapeutic agents that will assist us in the control of major and severe allergic disorders, particularly if we want to prevent severe drug and other reactions.

Dimetane® (parabromdylamine) (1-p-bromophenyl)-2-(2-pyridyl)-3-dimethylaminopropane maleate) was originally investigated by us in its current oral form, and it became evident that the parenteral use of this drug had a good potential. It was through the cooperation of the Department of Clinical Research of the A. H. Robins Company, Inc., Richmond, Virginia, that the injectable form was made available in two different strength ampules. A 1 cc ampule containing 10 mg of Dimetane per cc, and a 2 cc ampule containing 100 mg per cc were prepared for either intravenous or intramuscular use. There are distinct advantages in both of these preparations. For example, the 10 mg per cc ampules were considered particularly desirable for intravenous use, and the dosage could thus be adjusted without fear of overdosage. Should the physician desire to give a patient 20 mg, two 1 cc ampules could be used. The 100 mg per cc concentration ampules have a distinct value, particularly in the consideration of mixing this preparation with other drugs[1] in the same syringe, as with intramuscular penicillin,[9] the use of various allergenic extracts,[5,8] vaccines, and in blood transfusions.[2,10] Sanger, *et al*[8] in their study on the use of antihistaminic agents in unusually hypersensitive patients, found that these agents afford protection against the local inflammatory changes caused by the immunizing injections of allergens, and, in addition to this local reaction, it also offered a further protection against systemic reactions, particularly if larger immunizing and more rapid incremental doses were employed in the desensitization program. Other uses for intravenous antihistaminic agents in combination with other drugs were studied by Kearns,[4] Simon,[11] and Sanger,[7] especially with the use of intravenous urograms.

Bernstein and Klotz[1] showed in their recent experience that Chlor-Trimeton Injectable® offered a rather wide range of clinical usefulness when a rapid acting antihistanimic effect was needed, especially in the prevention of allergic reactions and drug reactions, in the treatment of urticaria, and for the relief of weeping eczema.

One of the most comprehensive studies dealing with a similar injectable

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antihistanic agent, Chlor-Trimeton Maleate Injectable® (100 mg/cc) was reported by Jenkins.[3] This study consisted of the use of this drug in some 226 patients for the purpose of determining its prophylactic value and therapeutic effect in allergic disorders. The author considered this preparation as a definite therapeutic adjunct in the symptomatic treatment of urticaria, angioneurotic edema, allergic rhinitis, poison ivy and food allergies. The effect was less effective in atopic dermatitis and bronchial asthma. Jenkins'[3] findings were similar to that of Bernstein and Klotz,[1] in that the drug quickly relieved weeping eczematoid eruptions and severe acute urticaria. The side effects from its use were few and consisted primarily of slight drowsiness, jitteriness or dryness of the mouth in 4 per cent of the cases studied. No sensitivities were observed in any of the patients.

There was a very close similarity between Chlor-Trimeton Maleate Injectable® (-1-p-chlorophenyl)-1-(2-pyridyl)-3-(dimethylaminopropane maleate) (chlorpheniramine maleate) and Dimetane Maleate Injectable®, which is a parabromdylamine maleate (-1-(p-bromophenyl)-1-(2-pyridyl-3-(dimethylaminopropane maleate). Figure 1 shows the chemical names and structural formulae of these two drugs.

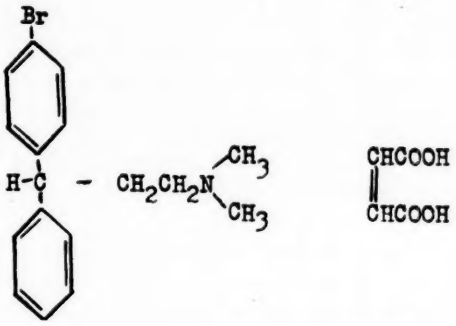
According to Murphey,[6] "You will probably be interested in the observation that the atomic weight of chlorine is 35.45 as compared to the atomic weight of bromine of 79.90. There is also a significant difference in the atomic radius or size of each of these atoms. The atomic radius of the chlorine atom is 0.97×10^{-8} cm as compared with the atomic radius of bromine of 1.13×10^{-8} cm. It is thus seen that the bromine atom is 16.5 per cent larger than the chlorine atom." He further postulates, "It is our interpretation that the presence of the bromine atom in parabromdylamine results in a molecule which is able to achieve a better or more secure fit on the receptor site, thus resulting in a more effective blockage of histamine on the cell surface, leading to a diminished manifestation of the typical response seen from the attack of histamine."

CLINICAL STUDY

In our current clinical study of twenty-five cases, we used both concentrations of Dimetane Injectable®, namely the 100 mg per cc or 10 mg per cc forms, employing them in the management of varied allergic manifestations, particularly in patients who were having severe symptoms. One case of erythema multiforme was included in the group.

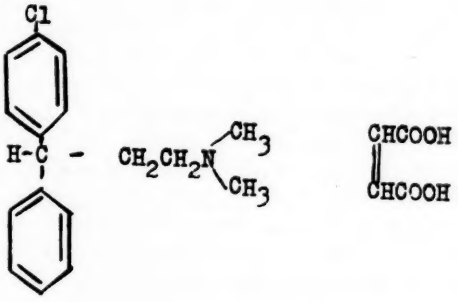
Table I is a summary table and shows a correlation of the cases according to decade, allergic or other manifestations, dosage response to treatment, side reactions, and remarks. Symptoms checked in bold face (heavy) type indicate the current manifestation for which the patient received the drug. Certain patients had multiple manifestations, particularly in instances of constitutional reaction, secondary to insect bite, characterized by

urticaria and angioneurotic edema, and those patients having drug reaction characterized by angioneurotic edema and urticaria plus a serum-sickness type of reaction.



Parabromdylamine Maleate

1-(p-bromophenyl)-1-(2-pyridyl)-3-dimethylaminopropane maleate



Chlorpheniramine Maleate

1-(p-chlorophenyl)-1-(2-pyridyl)-3-dimethylaminopropane maleate

Fig. 1. Comparison of Dimetane Maleate® with Chlor-Trimeton Maleate® according to the chemical names and structural formulae.

Table II shows the number of patients according to decade.

The only significant point to be made in reference to the number and age of patients is that the youngest patient was thirteen years of age. It was

TABLE I. SUMMARY OF CORRELATION OF TWENTY-FIVE CASES

Number	Name	Decade	Manifestation								Dose		Results			Side Reaction			Remarks
			Urticaria, Angioneurotic Edema	Allergic Rhinitis	Bronchial Asthma Bronchitis	Drug Reaction	Atopic Dermatitis	Hay Fever	Systemic Reaction	Miscellaneous	10 mg/cc Intravenous	100 mg/cc Intramuscular	Good	Fair	Poor or None	Drowsy	Dizzy	Other	
1.	T.J.B.	7	–	–	–	–	–	–	–	X	20	20	x			0	0	0	Control 12 mg b.i.d.
2.	R.W.B.	2	X	0	0	0	0	0	X	0	20		x			0	0	0	Control
3.	R.E.B.	3	x		x	x	X	x		x		15	x			0	0	0	Control 12 mg b.i.d.
4.	E.P.D.	4	0	X	x	0	0	0	0	0	20		x			Sl	0	0	
5.	J.H.E.	5	x	X	0	0	0	x	0	0		20	x			x	0	0	
6.	J.E.	3	X	0	0	0	0	0	X	0	20		x			0	0	0	Control
7.	C.V.E.	5	X	x	0	x	0	0	0	x	20			x		0	0	0	12 mg/8 hr
8.	M.M.F.	6	X	0	0	x	0	0	0	x	20	20	x			0	0	0	IM p.r.n. 12 mg t.i.d.
9.	A.H.G.	6	0	0	X	0	0	0	0	0		20	x			0	0	0	12 doses for cough
10.	T.W.H.	4	X	x	0	0	0	0	0	0		15	x			0	0	0	12 mg q.i.d.
11.	E.T.H.	5	0	0	0	X	0	x	0	x		20	x			0	0	0	6 doses
12.	W.H.	6	0	0	0	0	0	X	0	0		10	x			0	0	0	With pollen Rx
13.	L.K.	7	0	x	0	0	0	X	0	x		20	x			0	0	0	With pollen Rx 18 doses
14.	M.K.L.	4	0	X	0	0	0	x	0	x		20	x			x	0	0	12 mg b.i.d. Control G.I.
15	W.M.M.	4	0	X	x	0	0	x	0	0	20		x			0	0	0	
16.	C.R.N.	4	X	0	0	0	0	0	0	0		15	x			0	0	0	Control 12 mg b.i.d.
17.	W.F.R.	6	X	0	0	0	0	0	0	0	20	20	x			0	0	0	IM/8 hr 12 doses
18.	J.H.T.	6	X	0	x	x	0	0	0	0		20	x			0	0	0	12 mg b.i.d.
19.	E.T.T.	5	X	x	0	0	0	0	0	0		20		x		Sl	0	0	
20.	R.T.W.	5	0	0	0	x	X	0	0	x		20		x		0	0	0	Control 12 mg/8 hr
21.	M.E.W.	3	X	0	0	X	0	0	X		20		x			0	0	0	IM/8 hr x 9 then 12 mg/8 hr
22.	M.A.P.	5	0	0	0	X	0	0	X		20		x			0	0	0	Control itch and pain
23.	S.R.	3	X	0	0	X	0	0	X	0	20		x			0	0	0	Control itch and pain
24.	W.A.R.	4	0	0	X	0	0	0	0	0	20	20	x			0	0	0	Control of cough
25.	G.E.	2	X	0	0	0	0	0	0	0	3		x			x	0	0	Control A.N.E. of tongue

the author's belief that patients of any age group may be considered for treatment with this parenteral drug, provided there is no known antihistamine intolerance and that dosage is properly adjusted. In intravenous administration, the drug is well diluted and administered slowly.

Of the twenty-five patients under treatment, twenty-two showed a good response to treatment, as characterized by a satisfactory control of the immediate distress. In two patients with an allergic rhinitis, symptoms were alleviated; however, in instances of urticaria, the lesions did not in each instance disappear, but the symptoms of acute itching were adequately controlled. This was one of the most outstanding features of this survey, in that although the urticarial lesions frequently persisted, in a number of cases the patient who had been scratching and clawing himself, would, within a period of five minutes (particularly following the administration of intravenous parabromdylamine), obtain relief.

As regards reaction, there were three patients who became drowsy, and

it was necessary for them to sit down and remain in the office for a while. However, these patients were able to leave the Clinic or Emergency Room by cab. There were two other patients who experienced slight drowsiness of no real clinical significance. All patients who had been drowsy reported

TABLE II. NUMBER OF PATIENTS ACCORDING TO DECADE

Decade	Number of Patients
2	2
3	4
4	6
5	6
6	5
7	2

that they had appreciated a good response to the treatment. One patient who had been only slightly drowsy obtained a good response, and another patient who was slightly drowsy appreciated only a fair response to the treatment of his urticaria. Other antihistaminic agents, including Chlor-Trimeton® had been tried orally but with no significant response, and the patient did not respond to subcutaneous epinephrine HCl 1/100 (aqueous).

There were two patients in this series who received coseasonal pollen therapy for acute hay fever, and were given 10 mg of Dimetane® in the same syringe; in one instance 20 mg of Dimetane® was injected subcutaneously. Both patients were relieved of their hay fever without any side effects. The coseasonal treatments were repeated on several occasions and one patient received a total of eighteen of these combined treatments and was enthusiastic with the response she received.

There were a number of patients initially receiving either intramuscular or intravenous parabromdylamine, and subsequently placed on oral therapy with the 4 mg tablets or the 12 mg Extentabs, with dosage frequencies of four to twelve hours. In several instances when the patients were in distress, they received 12 mg as often as every six hours.

In one instance (Case 24), a patient was hospitalized because of a severe asthmatic bronchitis, and one of the most disturbing features of her condition was a severe and more or less continuous cough. This patient was initially given Dimetane Injectable®, 20 mg intravenously with satisfactory control of her cough. She was subsequently given 20 mg intramuscularly at eight-hour intervals. After one intravenous treatment and one intramuscular treatment, she was scheduled for her third dose of 20 mg intramuscularly at 11:00 P.M. Through error the nurse gave the patient 1 cc of 100 mg of Dimetane Injectable® intramuscularly. I was advised by telephone, and suggested to the resident physician that in the event the patient developed marked symptoms of drowsiness, tenseness, or other side reactions, she should be given epinephrine HCl 1/1000 (aqueous) subcutaneously or Ephedrine Sulfate, ¾ grains by mouth or by injection, and if she needed

a further stimulant to consider Caffeine Sodium-Benzoate. The resident physician advised me the next morning that the patient did not know that she had received the wrong dose of the drug. She did not develop any side reaction, nor any significant drowsiness. The only complaint she had

TABLE III. DIAGNOSIS AND NUMBER OF CASES TREATED

Manifestations	No. of Cases
Insect constitutional reaction with urticaria and angioneurotic edema	2
Atopic dermatitis	2
Hay fever	2
Perennial allergic rhinitis	4
Drug reactions	4
Urticaria and angioneurotic edema	8
Asthmatic bronchitis with severe cough	2
Erythema multiforme with ulcerative stomatitis and generalized pains	1
Total	25

some eight hours later was that her mouth was abnormally dry and that she was drinking a lot of water. This case illustrates the satisfactory way in which this patient tolerated an abnormally large dosage of parabromdylamine without any noteworthy side reaction, and also the apparent margin of safety of this drug.

Table III shows a breakdown of the various manifestations or diagnoses according to the number of patients treated. All of the patients had allergic reactions with the exception of one patient with erythema multiforme (Case 1) who complained of generalized aching and distress on swallowing. Her mouth was covered with multiple ulcerations about the gums, lips, tongue, and oropharynx, and she complained bitterly of extreme pain. She was given intravenous Dimetane Injectable® 20 mg diluted to 10 cc over a period of six minutes, and after receiving some 3 or 4 cc, the patient stated that she had already appreciated some relief of the painful mouth lesions, and by the time she had received the entire dosage of 20 mg intravenously, she reported that she could swallow, and had no further pain.

Case 21 was that of a young lady twenty-six years of age who had been treated for an acute bronchitis with Chloromycetin 100 mg intramuscularly followed by oral Chloromycetin 250 mg four times a day for a period of four days. Nine days following the initiation of this therapy, the patient developed recurrent urticarial lesions accompanied by itching, and twelve hours later these symptoms were worse. She was treated with Benadryl 100 mg every four hours, without response. She was given ACTH-Gel, 40 units twice daily, in four doses. I saw her on the thirteenth day after Chloromycetin was started, and she was acutely ill with symptoms of a delayed serum sickness type of drug reaction, extremely painful and swollen joints, multiple areas of angioneurotic edema and marked edema of the scalp and soles of the feet which were tender to touch, even with

bedclothing. She had previously received epinephrine HCl 1/1000 (aqueous) subcutaneously without significant response. At the time of her admission to the hospital she was given 20 cc of 5 per cent dextrose to which we added 20 mg of Dimetane Injectable®. The itching and burning rapidly disappeared while the Dimetane® was administered. Before we had given her half of the injection she began to appreciate some relief and by the time we had completed the total 20 cc (20 mg) dosage (a period of some ten minutes), the patient had no itching of the lesions about the joints and the scalp, although the swelling had not disappeared. These areas could be palpated without pain. She was given 20 mg of the drug intramuscularly every eight hours for a total of eight injections, and this was followed by oral therapy with Dimetane Extentabs® 12 mg every eight hours, in subsequent descending doses, resulting in adequate control of her swelling.

In many instances the blood pressure and the pulse rate were checked before, after, and during the administration of Dimetane Injectable® and in no instance was there any significant change.

Case 8 was one of the most severe cases of recurrent chronic angioneurotic edema and urticaria this writer has ever witnessed. The patient had edema of the oropharynx and tongue recurrently, marked edema of the cheeks, various joints of the body and of the bladder, which was observed by her urologist upon cystoscopic examination. She had a recurrent drug intolerance or allergy to a number of drugs including the sulfonamide drugs. There were multiple food sensitivities which the patient had identified and could precipitate exacerbations at will by eating such food. Her symptoms had been recurrent since April of 1953; and she first came under my care in October 1955; in view of the severity of the swellings, it became necessary for me to set up an emergency program by which this patient or a member of her family could, in an emergency, give her temporary relief, particularly when she had edema of the tongue and oropharynx. For some months we used a combination of epinephrine HCl (aqueous) 1/1000, 0.3 cc injected subcutaneously, and Chlor-Trimeton Injectable® 20 mg which she took by hypodermic during such periods of acute swelling. Subsequently, we started her on Dimetane Injectable® in April 1957, during which period of time she was hospitalized. She had been given other antihistaminic agents including Benadryl® 50 mg four times a day which made her dizzy, and she disliked the drug. She had been receiving Chlor-Trimeton® 20 mg intramuscularly which controlled the itching, and slightly improved the swelling. However, the patient reported that she was having some gastrointestinal distress following administration of the Chlor-Trimeton®, so we switched to 20 mg of Dimetane Injectable® intramuscularly every eight hours for a total of six doses. She seemed to have her symptoms under much better control. She was given 20 mg every twelve hours for four doses and after discharge from the

hospital, continued on 20 mg intramuscularly on such occasions as her symptoms warranted.

This has been given repeatedly on occasions, sometimes several times a day, and at other times as infrequently as once a month. She has had no side reactions from this drug which her daughter administered during periods of acute swelling. She has been maintained on Dimetane Extentabs® 12 mg three times daily for a number of months without any side effects and with reasonable control of the swelling. While she was on this maintenance dosage the patient observed that she could tolerate certain of the foods which had bothered her previously.

As a point of interest, this patient was formerly on varied steroid hormones for a period of some fourteen months without any significant response. Occasionally she did have some retention of fluids. However, she has had no steroid hormones in any form during the past year and is getting along fairly well excepting for recurrent bladder infections; due to her marked drug sensitivities and intolerances, her urologist was having a great deal of difficulty keeping the infection under control.

SUMMARY

A clinical evaluation of Dimetane Injectable® was carried out on twenty-four allergic patients, and one without any history of allergy, who suffered from acute erythema multiforme.

Several cases are reviewed, and the most noteworthy observation was the rapid response or alleviation of pain, itching and other distress following intravenous administration of the drug. There were three instances in which side reactions of drowsiness was experienced. Twenty-three of the twenty-five patients showed good results, and two showed a fair response to treatment. Of this group, all of the patients showed some response to the drug.

As a result of observations made in the administration of both the intramuscular and intravenous Dimetane Injectable®, it is felt that this drug has a good potential in the symptomatic relief of acutely ill patients such as those described.

A comparison of the structural and chemical formulae of both Dimetane Maleate® and Chlor-Trimeton Maleate® was made.

A partial review of the literature concerned with intravenous and intramuscular administration of certain antihistaminic agents has been made and correlated with this clinical study. Using this study as a basis, the author feels that a further consideration of the use of parabromdylamine injectable is warranted in patients presenting severe allergic reactions as well as with certain non-allergic problems.

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CHANCE AND LOGIC

"With one bold stroke Kepler ventured to forsake the ways of traditional thinking and try other forms of curves for the orbits of the recalcitrant planets. At length he tried the *ellipse*, and found that he could respresent planetary motion far more accurately than had yet been done in the history of astronomy. He announced the first fundamental law of planetary theory—that each of the planets revolve about the sun in an ellipitical orbit with the sun at one of the foci.

"He accomplished this by his incomparable energy and courage, blundering along in the most inconveivable way (to us) from one irrational hypothesis to another, until, after trying twenty-two of these, he fell, by the mere exhaustion of his invention, upon the orbit which a mind well furnished with the weapons of modern logic would have tried almost at the outset" (Charles S. Pierce. *Chance, Love and Logic*, New York, 1923).

THE TREATMENT OF POLLINOSIS BY MEANS OF A SINGLE ANNUAL INJECTION OF EMULSIFIED EXTRACT. V.

Preparation, Standardization and Administration

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THE techniques of preparing and standardizing extracts of pollen and of emulsifying and administering them in repository form, although undergoing continuous improvement, are at a stage at which they can be presented in detail. The history of recent developments in this field is brief.[1-5]

Universally (although in our area ragweed pollen is a general nuisance), grass pollen is the chief cause of hay fever. Because, in New England and in many other areas, the grass pollen season is sharply delineated and symptoms due to other pollens or house dust are only, if present, minor causes of difficulty, the results achieved in patients afflicted with grass pollinosis can be validated more easily. The following data refer therefore to grass pollen.

PREPARATION OF EXTRACT

Since commercial extracts containing glycerine will not emulsify, and because almost all, if not all, antimicrobial substances when dissolved in oil cause local reactions, extracts prepared with either cannot or should not be used although we have recently used, with no ill effects, 0.4 per cent phenol. To prepare an extract of grass pollen for repository injections, take 4 grams of each of the following (Soxhlet) ether-defatted pollens: June Grass (Poa pratensis); Sweet Vernal Grass (Anthoxanthum odoratum); Red Top (Agrostis albus); Orchard Grass (Dactylis glomerata); Meadow Fesque (Festuca elatior), and 5 grams of Timothy (Phleum pratense). These proportions may be modified according to local conditions.

Add 200 ml of Coca's Solution.[6] Extract for forty-eight hours at 4° C and, during the day, agitate frequently either by hand or mechanically. Then pass the extract through a Whatman No. 1 filter paper, using a glass or else a Buchner funnel. The filtrate is then refiltered by the use of a sterile No. 6 Seitz Laboratory Filter into a 500 ml filtering flask. The coarse and finely filtered extract is transferred, with a sterile pipette, to a sterile 400 ml storage bottle. Sterility is corroborated by inoculating (with 0.1 ml of extract) 15 ml of autoclaved Baltimore Biological Thioglyconate Medium. This same medium is used for testing sterility of the emulsion.

STANDARDIZATION OF EXTRACTS

The inconsistencies of the macro- and especially of the micro-Kjeldahl methods for estimating the potency of pollen extracts have been the

subject of a series of controversial communications too lengthy to list. These methods have therefore been abandoned by many allergists. In our experience, standardization on the basis of total nitrogen and protein nitrogen have been equally inconsistent when bioassayed by skin tests, in that extracts of the supposed same strength elicited reactions which varied greatly. In our hands, the weight/volume method of "standardization" has been equally faulty because batches of pollen of equal weight have been proven to be unequally reactive. Although I would be the first to concede that the so-called protein nitrogen unit is probably neither all protein, nor all nitrogen, or, for that matter, a "unit,"[7] nevertheless with modern photoelectric methods of standardization, not subject to the vagaries of the older now widely discarded procedures, we have for fifteen years, on the basis of standardizing extracts in such protein nitrogen units, been able to prepare extracts of consistent potency and excellent interchangeability, although they do not contain the complete antigen needed for hyposensitization of all patients.

The reagents required are (a) Coca's Solution *(op. cit.)*; (b) phosphotungstic acid, 20 per cent; (c) sulphuric acid, 20 per cent; (d) phosphotungstic-sulphuric acid wash solution (one part, 20 per cent phosphotungstic acid, one part, 20 per cent sulphuric acid, and ten parts distilled water); (e) special acid digestion mixture, [distilled water, 54.0 ml, sulphuric acid, (concentrated), 35.0 ml, phosphoric acid (85 per cent), 10.0 ml, and perchloric acid (20 per cent), 0.5 ml],[8] and (f) Nessler's reagent.[9]

The nitrogen stock standard (1.0 mg/1.0 ml) is made from pyridine-free reagent grade ammonium sulfate which has been dessicated over concentrated sulphuric acid or else heated at 100° C for eight hours. It is weighed as soon as cooled, usually in thirty minutes. Exactly 4.716 grams is dissolved in ammonia-free water and transferred quantitatively with several rinsings to a one-liter volumetric flask and then taken up to volume with more ammonia-free distilled water. When 10.0 ml of this stock solution is diluted volumetrically to 100 ml with additional ammonia-free water dilute nitrogen standards of 0.05, 0.1, 0.15, 0.2, and 0.25 mg/ml are easily obtained.

The only special apparatus required is a monochromatic Bausch and Lomb colorimeter which must be recalibrated for each new lot of Nessler's reagent, and some Brown-Benotti bump-proof digestion tubes,[10] obtainable from the Fisher Scientific Corporation, Greenwich and Morton Streets, New York 14, New York. With the use of the standard straight tubes, bumping causes loss of the extract being standardized. It was for this reason that, in 1941 the bump-proof tube was invented.

Put 1.0 ml of the diluted extract of unknown strength into a 15 ml centrifuge tube and add 0.1 ml of 20 per cent phosphotungstic acid and 0.1 ml of 20 per cent sulphuric acid. Tap the bottom of the centrifuge tube gently until the solution is thoroughly mixed. Let stand twenty minutes. In order to wash down any particles of precipitate which may remain on

the inside wall of the centrifuge tube and above the level of the acid solution containing the precipitate, gently wash down, using a wash bottle or pipette, the inside walls of the centrifuge tube with no more than 3.0 ml of the dilute phosphotungstic-sulphuric acid solution. Place the tube in a metal centrifuge cup. Balance the cup on a trip scales. To pack the precipitate centrifuge at 25,000 RPM for twenty minutes.

At the end of centrifugation, again without disturbing the packed precipitate, pour off the supernatant fluid.

At this point the precipitate may be washed with 3.0 ml of the dilute phosphotungstic-sulphuric acid solution and recentrifuged. To drain, gently invert the centrifuge tube on filter paper. Allow to stand for five minutes. Into the righted tube put two to four drops of 1 N. NaOH. Tap the tube gently until the dissolved protein in the precipitate is thoroughly mixed with the sodium hydroxide.

By means of a wash bottle or a pipette and using no more than 3.0 ml of distilled water, transfer the protein solution quantitatively to a Brown-Benotti digestion tube *(op. cit)*. Add 1.0 ml of acid digestion mixture. Add two chemically clean 3 mm glass beads. Mix. Boil over a micro-gas burner. When the characteristic white acid fumes appear, cover the mouth of the digestion tube with a watch glass or a special glass bulb with tip, (available from Boston Medical Laboratory, 19 Bay State Road, Boston 15, Massachusetts) which fits into the mouth of the digestion tube. Boil gently until the solution is colorless. Remove from the flame and let the solution cool for approximately one minute. Remove watch or glass bulb. Add distilled water to the 35 ml mark on the Brown-Benotti digestion tube.

Mix, with no loss of solution, by twirling tube. Place tube in ice water for ten minutes or refrigerate for thirty minutes. Using a 15 ml Folin-Wu pipette, quickly add Nessler's reagent. Apply a clean rubber stopper. Invert to mix. Since it is important that the color development be carried out both in the unknown and in the reagent blank under as nearly identical conditions as possible, place the unknown aside until a reagent blank is prepared.

To prepare the reagent blank, pipette into a second digestion tube 1.0 ml of the acid digestion mixture. Add distilled water to the 35 ml mark. Add two chemically clean glass beads. Cool for twenty minutes and quickly add 15.0 ml of Nessler's reagent. Stopper the tube and invert to mix.

A colorimeter tube filled with the reagent blank is placed in a Bausch & Lomb monochromatic colorimeter and set at zero density, that is, 100 per cent transmission. The colorimeter has been calibrated using a 430 MU filter, against known nesslerized nitrogen standards of 0.05 mg N/ml, 0.1 mg N/ml, 0.15 mg N/ml, 0.2 mg N/ml, and 0.25 mg N/ml. The nitrogen curve in this case is represented by a straight line plotted on semi-logarithmic paper for use with photolometers and spectrophotolometers, the

percentage transmission being the abscissa of the graph and mgs N/ml being the ordinate.

Remove the tube of reagent blank from the colorimeter and replace with the tube containing the solution of unknown strength. A reading is taken. Having determined the percentage of transmission of the solution of unknown strength, now determine from the graph the number of mgs PN/ml of the aliquot portion of the extract. Correct for the dilution factor, if any.

For example: If a transmission reading of 46.5 per cent of the solution of unknown strength corresponds on the calibration curve to 0.130 mg N/ml, and the aliquot portion of the extract was 2.0 ml of a 1/10 volumetric dilution, the correction would be as follows:

$$0.130 \times \frac{10}{2} = 0.65 \text{ mg PN/ml, or } 65{,}000 \text{ PNU/ml}$$

(0.00001 mg PN/ml representing the equivalent of 1 PNU/ml)

With experience one learns to take an aliquot portion of the extract which, with the phosphotungstic acid, will precipitate no more protein nitrogen than can be digested completely by the acid digestion mixture and which will give a transmission reading between 30 to 60 per cent on the calibration curve of the colorimeter.

PREPARATION OF EMULSIONS

The emulsion originally described by Freund and McDermott (*op. cit.*) consisted of an emulsifying agent, Falba, and mineral oil, Atreol. The Falba consists of oxycholesterins extracted from lanolin, with beeswax and paraffin oils of varying density. It is available from Pfaltz and Bauer, New York, New York. The Atreol No. 9 is a mineral oil obtainable from the Atlantic Refining Company, Newark, New Jersey. Of Falba, melted in a water bath and transferred by means of a warmed, but not hot, high viscosity pipette, 1.0 ml was added to 1.5 ml of Atreol No. 9 U.S.P. The Falba melts at 212° F and the mixture can be autoclaved at 120° C at 15 pounds pressure for twenty minutes in a tube capped with a paper flask hood and held in place by an elastic band. Rubber stoppers must not be used with oil mixtures. Higher temperatures destroy the emulsifying action of the Falba and cause, as well, the formation of degradation products of the mineral oil. Since steam does not penetrate the oil, such autoclaving obviously represents simple heat sterilization.

We now use as an emulsifying agent, Arlacel A, a mannide monooleate, prepared by the Chemicals Division of the Atlas Powder Company, Wilmington, Delaware (and graciously furnished by Dr. Robert S. Rose of the company). It is a non-ionic partial ester surface active emulsifier. The Arlacel A, especially prepared for vaccines, must pass the biological tests set up by Salk as conducted at the University of Michigan School

of Public Health. It has so far been used in the inoculation of more than 75,000 military and civilian personnel by the Armed Forces Epidemiological Board of the Department of Defense.[11]

Instead of Atreol, we use Drakeol, obtained from the Pennsylvania Refining Company, Butler, Pennsylvania. This oil can be Seitz filtered. Salk (*op. cit.*) originally used one part of Arlacel A and nine parts of Bayol F (instead of Drakeol) sterilized by autoclaving at 15 pounds at 120° C for fifteen minutes. We also use these proportions, making 10.0 ml batches consisting of 1.0 ml of Arlacel A, and 9.0 ml of Drakeol (instead of Bayol F).

To her mixture of Falba, 1.0 ml and Atreol, 1.5 ml, Loveless added 0.5 ml of extract (60,000 P.N.U./ml). Using a 1 ml syringe, the tip of which touched the bottom of the tube, the three components were "pumped" by hand at the rate of ninety strokes per minute for five minutes. With slower pumping, the emulsion was incomplete, and longer or faster pumping often caused syneresis. Obviously the emulsion was only formed as a result of the turbulence experienced by the three ingredients as they passed through the opening in the hub of the 1 ml syringe. The mixture in the barrel served only as a reservoir, the plunger forcing the partially emulsified mixture in and out of the syringe and into the tube. Emulsion wastefully coated the outside surface of the syringe and the inside of the tube, resulting in a loss of 20 per cent or more of the mixture. Contamination could occur. The method served a useful purpose when few patients, namely, 117 in all, were being treated annually during the experimental stages of repository injection treatment.[12]

In our laboratories has been devised an easily sterilized, completely closed system emulsifier. It is a modification of a technique invented by Chase[13] who used 5 cm lengths of polyethylene tubing (No. PE 190) and two Clay-Adams female Luer-Lock adaptors (No. C-2625).

The polyethylene tubing ingeniously served to extend the length of the area of turbulence and the two syringes closed the system. But the tubing could not be autoclaved and had to be washed free of the bacteriostatic solution in which it was stored.

As the photographs show, a second hub was silver soldered to the pointed end of an 18-gauge needle. Using another blunt end ordinary 13-gauge needle, the three ingredients, namely 2.0 ml of the Arlacel A and Drakeol mixture described, and 2.0 ml of extract (20,000 P.N.U./ml) are drawn up into a 10 ml Luer-Lock syringe. The total of 4.0 ml represents 10,000 P.N.U. of extract in each milliliter. (Fig. 1) The 13-gauge needle is detached and one hub of the micro-emulsifier is attached. Slight pressure on the plunger fills the micro-emulsifier, expelling all the air. A second 10 ml Luer-Lock syringe with plunger well seated is attached to the free hub. (Fig. 2) With thirty to fifty strokes successfully slowly filling and emptying both syringes, an elegant emulsion results. (Fig. 3) One empty 10 ml syringe can be detached and replaced by successive empty 1 ml syringes

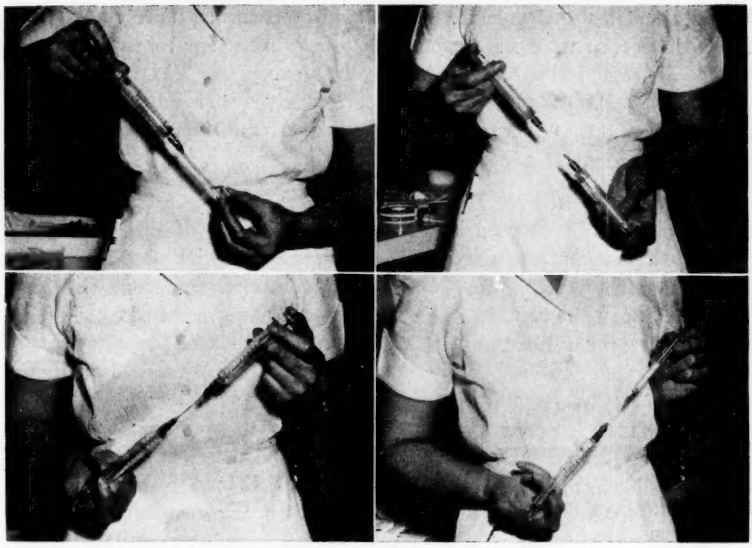

Fig. 1. (*left above*) Drawing up mixture of extract, ethylnorepinephrine, saline, and Arlacel A—Drakeol mixture.
Fig. 2. (*right above*) Emulsifier assembled.
Fig. 3. (*left below*) Emulsion completed.
Fig. 4. (*right below*) Loading a 0.1 ml syringe for administration.

which can easily, without contamination, be filled. (Fig. 4) The emulsion so stored will maintain its integrity for months, but in case of doubt can be re-attached to the emulsifier and attached to another syringe and re-emulsified. We cannot, however, break the emulsion down by centrifuging at 25,000 RPM for thirty minutes, thereby proving its stability.

We have for some time used a second modification of this technique. Drawn up are 2.0 ml of the Arlacel A-Drakeol mixture, 1.0 ml of extract (40,000 P.N.U./ml), 0.4 ml of epinephrine, 1:100, or of ethylnor-epinephrine 1:50 (Bronkephrine, Breon), and 0.6 ml of saline. Each milliliter of emulsion now contains 0.15 ml of epinephrine (1:100) or ethyl-norepinephrine (1:50) which, in emulsified form cause no palpitations, tremor or other signs of epinephrine side effects.

We have also used emulsions containing no epinephrine, but instead, in each 4 ml, either 0.2 ml of chlorprophenpyridamine (Chlor-Trimeton, Schering), 20 mg, or 0.8 ml of prednisolone 21-phosphate, so that, when 1 ml is injected of whatever strength of extract is chosen, the patient also receives 5 mg of chlorprophenpyridamine and 4 mg of the prednisolone compound.

At an early stage of emulsion injection treatment it was realized that a patient whose total dosage was to be 2,500 P.N.U. received 0.25 ml, while he whose dose was 10,000 P.N.U. received 1.0 ml. In other words, although the more sensitive patient received the smaller dose, it was given

him in a smaller total volume. This would be absorbed more quickly, the opposite effect of what was desirable. We now make emulsions containing 2500, 5000, and 10,000 P.N.U./ml, so that, except for the patient whose dose is 7500 P.N.U., and who therefore receives 0.75 ml, all injections total 1.0 ml and the absorption time is constant, less being absorbed in each unit of time for the more sensitive patient.

TESTING EMULSIONS

Syneresis can be checked by five methods. A drop of the emulsion is placed on a slide and examined microscopically by the high power lens. All drops should be equally minute and uniform in size. A second slide can be pressed upon the first, in which case the spreading will make the liquid phase, if present, visible. A drop of the emulsion can be placed upon the surface of water in a beaker. A well-made emulsion will maintain sphericity. Lastly, a drop can be added to oil, free of water, in which case the liquid phase, if present, is obvious to the naked eye, or, if the tube is centrifuged at 25,000 RPM for ten minutes, the droplets of water coalesce and are visible at the bottom of the tube. (I am indebted to Dr. Merrill W. Chase for making available to me his detailed knowledge of emulsion chemistry.)

The fifth test, a biological one, consists of using a drop of the emulsified 20,000 P.N.U./ml extract for a pressure puncture or scratch test in a patient who has proven himself sensitive at this level. A positive reaction proves the presence of a dispersed phase of the emulsion. With the Arlacel A-Drakeol mixture, we have not been able to elicit such reactions, although we have with the most perfect Falba-Atreol emulsions.

It is obvious that if the solution contains 20,000 P.N.U./1 ml, of which 90 per cent is in emulsion, then the remaining 1 per cent represents 200 P.N.U. An extremely sensitive patient might not respond to this by pressure puncture test, and yet would receive half of this amount in a dispersed phase if his total dose were 10,000 P.N.U. It is more likely that a pressure puncture positive patient would receive a total dose of 2500 units, and the dispersed phase would therefore equal 25 units, too little to cause a pressure puncture test, and yet enough to elicit a systemic reaction. It is because we cannot test emulsions for perfection beyond 99 per cent that we protect patients by five methods: ephedrine and an antihistaminic agent by mouth; epinephrine proximal to the site; and an antihistaminic agent and prednisolone in the emulsified extract.

There is here much more involved than the simple coating of minute droplets of extract with various types of mineral oil and emulsifying agents. The oil is not wettable and is not affected by electrolytes. The emulsion is not elastic (cannot be stretched), will not coagulate, and will not swell. In a properly made emulsion there is no liquid phase, in that all of the aqueous droplets are suspended in a continuous phase of mineral oil.

Extract can only be released as macrophage cells remove the oil coating

of the individual component droplets. The total amount so available is more minute than that represented by any ordinary injection. It is, of course, related to the area represented by the total surface of the droplets of which only those touching the tissues can be attacked. This surface area gradually diminishes in size. The contents of those droplets not in contact with macrophage cells are not released. There is therefore continuous slow absorption beginning at levels lower than the smallest hypodermic injection of extract in saline. It would appear that patient tolerance gradually increases by the time the last part of the extract has reached the tissues.

In no patient has local swelling been seen within seven days. It rarely lasts more than two or three days.

Work in progress concerned with the rate of absorption, using instead of extract, other substances whose presence in the blood stream can be measured will serve to demonstrate exactly how long such absorption takes.

Blocking antibody studies to the contrary, there is no adequate present-day proof that with pollen extracts, slow absorption is associated with greater hyposensitization (as compared to safety) or that with complete absorption the formation of antibodies ceases. But such proof is equally lacking for extracts prepared in saline and injected in the usual way, to be absorbed within seconds. But, until such proof is presented, no other present-day injection technique makes pollen extract available to the tissues in such small quantities so slowly and for so long a time. The apparent size of the total dose injected is a matter of secondary importance.

Other work in progress is also concerned with the preparation of much finer emulsions with larger numbers of component droplets with ever slower and therefore safer speeds of absorption. Although perhaps greater safety has been gained, it remains to be seen whether too slow an absorption is not as much to be avoided as that which is too speedy.

The question might be legitimately asked that, if the emulsion does all that it has been described as doing, why then do we "protect" our patient? In the beginning we used Atreol and Falba and prepared the emulsion by "pumping." The droplets were not and could not be made uniform, and in some cases we did not know how much of the dispersed or watery phase was present. The reaction rates published by Loveless (*op. cit.*) appeared to be excessive until it was realized that the percentages noted were high but the actual number of reactive patients was low, in that the total number of patients treated was so small.

We could slow the absorption of such dispersed phases by either adding epinephrine (1:100) or ethylnorepinephrine 1:50 (Bronkephrine, Breon) to the extract or else by injecting either drug proximal to the proposed site of the injection, or do both.[14] We could obviate some possible reactions by the use of prophylactic antihistaminic agents. These precautions, widely misinterpreted, were not followed because the injection was not safe, but rather, despite its safety, doubly to protect the patient and, from a medico-legal point of view, the physician. In the past, whenever a reaction

occurred following the injection of extracts in saline, the same procedure (but after the event) was always followed. All I did was to use it before a possible reaction could take place, although none were expected and those few which occurred could, in almost every case, have been predicted and avoided. After twenty-five years of giving extracts in saline, I continue to protect patients of this same degree of sensitivity by adding epinephrine (1:1000) 0.1 to 0.3 ml to every injection of extract in saline, and for the same reasons.

TESTING THE PATIENT

The skin test techniques are those familiar to all physicians in the field of allergy. For the standard scratch, punch, or pressure puncture test, a solution of 20,000 P.N.U./ml in 50 per cent glycerine serves. For intracutaneous tests, we use solutions of 10, 100, 1000, and 2000 P.N.U./ml.

The conjunctival tests are done with extracts free of glycerine. The successive dilutions can be doubled or the nearest whole numbers can be used, as 5, 10, 20, 40, 75, 150, 300, 600, 1200, 2500, 5000, 7500, 10,000, 15,000, and 20,000 P.N.U./ml.

One measured drop, 0.03 ml, is placed on the everted lower lid and on the spot devoid of nerve supply and of sensation. This is about a quarter inch from the inner caruncle.

The technique was first described by Dunbar[15] and perfected by Noon[16] and by Freeman.[17] We use a one-eighth ounce bottle with the ophthalmic type of dropper, available from Arthur H. Thomas Company, Philadelphia, Pennsylvania (as bottle No. 2253-K and dropper assembly 2253-A). The drops are slightly larger than those obtained with a syringe and needle (0.02 ml), but with good technique, uniform. Caruncular injection is apparent within a period of five to seven minutes. Should it not appear, a drop of the next succeeding strength is similarly instilled. When injection does appear, the instillation of the next successive strength into the other eye confirms the positive test. The conjunctival sacs are then flooded with saline and into each several drops of epinephrine 1:1000 are placed. In some patients sneezing and coryza of the nostril of the side of the eye tested is noted. In some there are no positive conjunctival tests.

Regardless of all arguments to the contrary, a patient may not present a positive conjunctival test and yet be extremely sensitive to both pollen and to other allergens.

It has long been known, for example, that the conjunctivae may be completely non-reactive to pure undiluted horse serum, the injection of which has subsequently been associated with immediate anaphylactic shock. And yet, there is a relationship between the positive test and the reactivity, in that Kojis[18] has shown that when the conjunctival test was positive to such serum, the incidence of serum sickness was five times greater, and that of anaphylaxis, 173 times greater than when the test was negative. Peshkin[19] has, on the contrary, observed that positive ophthalmic tests may occur in patients who do not react to skin tests. But, then again, as had

Noon shown in 1911 (*op. cit.*), Tuft[20] has reported positive eye and skin tests in patients not subject to pollinosis. A typical history with a positive skin test is sufficient for most allergists. An eye test or else a nasal insufflation, that is, a test with pollen itself or pollen extract, is more than enough corroboration.

For just as long as we remember that a positive skin test is a purely fortuitous event and a negative eye test equally so, when no ocular symptoms result from exposure to pollen as in pollen asthma, we will not mistake the degree of positive tests, crude in the extreme as representing *pari-passu* degrees of clinical sensitivity. The fact that millions of patients have been treated safely on the basis of such tests is an indication only of what the human frame can endure, and is in no sense a proof of the validity of the test.

The fault does not lie in giving an injection of pollen extract to a patient who is not pollenotic, but rather in not treating a patient with true pollinosis with the other minor causes of symptoms which may become apparent only when the major masking cause, the one striking sensitivity to one pollen has been treated. The failure is usually laid at the door of insufficient hyposensitization.

It has also, in the past, been said that failures in treatment, partial or complete, were due to the small total dosage injected. The failure is probably caused by the sensitivity of the patient, who for this reason receives the smaller dose. A larger dose, when it can be tolerated does not make him well because it takes so little pollen to make him sick. And what is more, there are patients who do not respond to injections of pollen extract however administered and in whatever dosage. In these it is only honest not to continue courses of useless injection treatment but rather to treat them symptomatically.

Examination of the original paper upon which the structure of present-day multiple injection treatment is based illustrates several points: Noon's paper (*op. cit.*) merely describes the effect of injections of pollen extract upon the ophthalmic reaction, but Dr. Freeman's paper (*op. cit.*), (soon to be published in these pages as an Historical Document), deals with only twenty patients. Two were seen on only one occasion. Six were seen, in all, for one month, seven for two months, two for three months, and one from July, 1910 to May, 1911, and another from September, 1910 to May, 1911. The highest dose injected (one patient) was 2000 Noon units. The others received, one patient, 2 units; one, 3 units; one, 5 units; two, 6 units; three, 10 units; one, 15 units; one, 18 units; two, 20 units; two, 25 units; one, 50 units; one, 100 units, and one, 120 units. The results seen in sixteen of the twenty patients were judged either to be "just satisfactory" or else "moderately" or "fairly" or "eminently satisfactory."

Referring to the conjunctival test and injection treatment, Dr. Freeman says, "It is perhaps possible by the ophthalmo-reaction to detect three stages in immunization. In the first stage, favorable doses are followed by

an immediate rise in resistance, but should not be followed by an increase in the size of the next inoculation. In the second stage, a larger dose is required, giving first, a slight negative phase followed by a slow rise in immunity. In the final stage, the eye reaction becomes stationary but apparently the dose may be increased with advantage so long as there is no evidence either laboratory or clinical, of an overdose."

"Owing to the nature of hay fever," writes Dr. Freeman in regard to rule-of-thumb injections, "there is no danger to life and only temporary danger to health by inoculating 'blindly'—i.e., without controlling the doses by ophthalmo-reactions, but it is thought that in order to make a diagnosis and to fix the first dose, at least one eye testing will be necessary."

It will be noted that this paper is based upon conclusions drawn from observations of a "series" of eighteen patients who by present-day standards were undoubtedly inadequately treated. There were no controls and since none received placebos, included were undoubtedly a number of "placebo reactors." No double-blind technique was considered necessary. The patients were taken in succession. There was no spurious randomization. None of these maneuvers can, it is obvious, reinforce or replace a brilliant clinician's observations long since confirmed by thousands of papers.

Our own rule-of-thumb (and in the present state of allergy practice, it is only that!) is to attempt to give patients who do react conjunctivally to strengths up to 80 P.N.U./ml a top dose of 2500 P.N.U. This is divided into three to five parts injected intramuscularly into the same site. If a local swelling occurs at any point, as it occasionally does, then no further portions of the proposed dose are given. This procedure, followed as well for the other patients on schedules to be described, accounts for the range of doses from 500 to 10,000 P.N.U. noted in previous papers in this series.

We have also given a number of patients of various levels of sensitivity doses not based on the magnitude of the ophthalmic and skin tests. In most cases (paper in press) the less sensitive patients as noted did better, although higher doses appeared to be indicated.

Positive conjunctival tests obtained with solutions ranging from 150 to 600 P.N.U./ml suggest that a total dose of 5000 P.N.U. can be tolerated. The patients reactive at 1200, 2500 or 5000 P.N.U./ml have successfully taken injections of 7500 P.N.U., and those at higher reactivity levels or giving no positive conjunctival tests take 10,000 P.N.U. or more. But as the studies continue, we depend less and less upon the conjunctival response and more and more on the skin test.

The empirical equivalents in skin tests are 2500 P.N.U. or less for a pressure puncture positive test; 5000 P.N.U. for a 10 or 100 P.N.U./ml intracutaneous positive test, with the 1000 P.N.U./ml positive test patient given 7500 P.N.U. and the 2000 P.N.U./ml responsive patient taking 10,000 P.N.U.

With the improved emulsion and slower absorption time and allowance for the fact that the systemic reacting patients have, in the past, demon-

strated either pressure puncture or 10 P.N.U./ml intracutaneous positive skin tests, or when positive conjunctivally have reacted below the 300 P.N.U./ml level, it appears that all patients can, on the basis of previous studies, tolerate more than we thought, and on the basis of work in progress achieve good results with smaller total doses. It may be said that we are, by this selection, ruling out the more sensitive patients. But these are, in any case, the patients who do poorly with multiple injection treatment.

As long as it is realized that there is neither rhyme nor reason behind the classical tables or groupings of patients for multiple injection treatment and as little for the present classification, the door will remain open for the study of possible relationships of dose to clinical (or qualitative) or to immunological (or quantitative) responses. Any dose to which the patient responds with relief is ideal for him and no dose is ideal for the patient who does not so respond. The percentages of successes and of failures are approximately the same in each group.

PATIENT PROTECTION

It is always good policy to protect the patient against the possible untoward effects of any injection of any substance. In an attempt to measure how far she could go in dose levels using her emulsion of Falba and Atreol, Loveless purposely protected no patients. In seventy-eight subjects treated for 1958 (personal communication) there were only two mild systemic reactions. Had each patient required fifty injections to reach the same dose, the corrected reaction rate would be 78 x 50, approximately one in 4000 injections. Loveless now adds epinephrine base to the emulsion.

In my desire to corroborate her clinical results and learn whether the mineral oil emulsion measured up to our other emulsion studies, we not only used material supplied by Loveless for the first thirty-eight patients, but, in addition, sedulously followed for the succeeding three pollen seasons the exact techniques described by her. The only major change made was the protection of the patient and the grouping of the patients into four classifications instead of three. The minor modifications have been described *(op. cit.)*.

At present, and only for medico-legal purposes, we administer to repository patients, as we do to multiple-visit patients, either parabromdylamine maleate, 4 mg, (Dimetane, Robins) or isothipendyl hydrochloride, 12 mg, (Theruhistin, Ayerst) or d-Chlorpheniamine, 2 mg, (Polaramine, Schering). As with extremely sensitive, multiple-injection patients, any antihistaminic agent would probably do. The patients who receive multiple-visit type of injection treatment of extracts in saline are also given epinephrine, 1:1000 (0.1 to 0.3 ml) mixed with their extracts. In patients on repository injection regimens, epinephrine, 1:1000, 0.1 ml is injected proximal to the proposed site of the repository. At present as noted, 0.3 ml to 0.6 ml of epinephrine, 1:100 or ethylnorepinephrine, 1:50 (Bronkephrine, Breon) is added to the extract and incorporated in the

emulsion. Any dispersed phase, if present, must therefore consist of at least 50 per cent of a vasoconstricting, bronchodilating agent. It should be emphasized that the precautions employed differ in no way from those used by thousands of allergists who treat tens of thousands of extremely sensitive patients by means of multiple injections of extracts prepared in saline.

ADMINISTRATION OF THE EMULSION

The skin over the insertion of the deltoid muscle is marked with a dot of Merthiolate®, used only for coloring purposes. The injection is given intramuscularly. The plunger is, of course, withdrawn to make certain the needle point has not breached a vein. The portion of the injection previously decided upon is given, with the syringe turned slowly on its vertical axis to spread rather than tear the tissues. When the needle is withdrawn, the patient presses his finger (no gauze, please!) on the spot to occlude any local vessels the needle may have traversed; to prevent escape to the surface of the emulsion injection and because it gives him something to do while waiting for the next part of the procedure. Almost all patients are just as bored with the single as with the multiple injection treatment, and despite its painlessness and speed, cannot wait to get away, to return in twelve months.

DATE OF TREATMENT

The majority of Loveless' total of 117 patients were given in all, over a period of ten years, 749 ragweed repository, placebo and extracts in saline injections administered during May or June *(op. cit.)*, none being given until the 1958 season after July first. For 1958 we treated, between April 14 and August 27, 684 patients afflicted with ragweed pollen sensitivity. It appears from our studies, to be published, that the period from June 1 to August 10 is the ideal time for treating ragweed pollinosis, although a number of patients treated during early May and after August fifteenth did well. In our area, grass pollen patients are treated between February first and June tenth.

Since systemic reactions are usually minimized by giving the patient an antecedent antihistaminic agent, or by adding epinephrine to the material in the syringe, or else are treated, when they occur, by the subcutaneous injection of epinephrine proximal to the injection site, absorption of which is delayed by a tourniquet, we have, by the technique outlined, given the patient the same treatment prophylactically that he would have received therapeutically. Some of, but not all of, the reasons have been outlined. There are others.

The population is drawn from a "cohort" of patients who have in more than half their number proven themselves, both in our hands and in those of others, systemically or locally markedly reactive to extracts prepared in saline. Many of these patients cannot be coerced into submitting themselves to conventional treatment. It was for this reason that we could

report on so many previously untreated patients whose symptoms had been present for so many successive years. They were, therefore, ideal "controls." Others were limited in the time needed for the most efficient multiple injection program. Some travel extensively and cannot take treatment with the requisite regularity. The responsibilities of some, especially mothers with large families, faced with the problem of a weekly, daytime baby sitter, made them ideal subjects for single, annual injection treatment. The cloistered, the crippled, those mentally and physically normal except for seasonal allergy, all three wanting the minimum medical attention, found single injection treatment desirable. For the patient of moderate circumstances and for the child who must be forced to accept the weekly injections, however skillfully given, repository injections solve the problem.

In 2,506 patients given one to eight repository injections, only twelve systemic reactions, however mild, have been recorded. Two others were certainly hypothetical and consisted only of an increase of nasal symptoms, present also before the injections. Five occurred in unprotected patients of whom two untreated but sensitive to grass pollen were given ragweed pollen repository injections during the peak of the grass pollen season. The three others occurred also in the only unprotected tree pollen sensitive patients of a second series of 326 patients. These three received the Atreol emulsion. They had reacted at the level of 75 P.N.U./ml ophthalmically in one, 150 P.N.U./ml in the second and also at 150 P.N.U./ml in the third. Five systemic reactions were noted in 446 grass pollen sensitive patients. They had demonstrated positive opthalmic test levels at 20 P.N.U./ml in two, at 40 P.N.U./ ml in one, at 80 P.N.U./ml in another and at 300 P.N.U./ml in the fifth. The other two systemic reactions occurred in a group of 684 patients treated with repository injections of ragweed pollen. None had occurred in a first series of 164 tree pollen sensitive patients. The sensitivity of these patients were all of the same order of magnitude. All of these reactions occurred with the use of the Falba-Atreol menstruum. So far, no systemic reactions have occurred with the patients given pollen extracts emulsified in the Arlacel A-Drakeol mixture.

If in round numbers we take only the pollen sensitive patients so far described, approximately 1500, and postulate that each took only one repository injection and that this represents a hypothetical fifty injections in saline to reach the same level of dose, the repository injections are equal to 75,000 injections of extract in saline, that is, one hundred injections daily for a period of two years. It is doubtful that any physician, however cautious, could give this many injections to patients of such manifest sensitivity and not encounter so few reactions of the type seen.

Each patient responded to additional epinephrine injected into the opposite arm (0.3 ml, 1:1000) and oral or intramuscular antihistaminic agents.

No patient who has experienced a systemic reaction has planned to cease treatment, suggesting that to the patient, at least, first, the reaction was not alarming and second, the results were obviously worthwhile. In the beginning of the present study, complaints of the drowsiness caused by the antihistaminic agent used and of the jitteriness due to the injection of epinephrine were far more numerous and more disturbing. Patients receiving their fourth to eighth repository injection often request that no antihistaminic agent or epinephrine be given them.

OTHER REACTIONS

In the patients treated with pollen extract, three "cold" abscesses occurred. From none could bacteria be cultured. All broke down spontaneously and healed without sequelae. We have had an exactly equal number in patients treated with extracts in saline.

"Swellings" were noted in fifty-eight of 725 repository injections of lyophilized house dust. This reaction, seen only during the early days of treatment, is a function of the magnitude of the dose. Of these, thirteen needed no medical attention, absorbing slowly of themselves. The contents of twenty-six were aspirated. In eight, the injection of prednisolone 21-phosphate (40 mg) resulted in immediate healing. The others "broke down" and again, slowly healed of themselves. None have so far developed in patients given, as a first injection, less than 1.06 mg of the lyophilized material. These patients, who present special features such as delayed or "Koch type" skin and eye reactions, will be the subject of a separate communication.

RESULTS

The hypothesis that a patient could be given a dose of extract probably just below his limits of tolerance has forced us to change some of our standards of the treatment of pollinosis. With the major pollen not causing difficulty, symptoms occurring during the respective pollen seasons, and in the past presumed to be due to the major pollen, can be proven to be caused by apparently minor allergens. Patients sensitive clinically to either tree or grass pollen and sensitive by skin test to the other, will often demonstrate symptoms only when both are prevalent. This holds equally true of either the grass and the plantain pollen sensitive patients and is quite obviously seen in the patients sensitive to ragweed pollen and to house dust. Those treated for ragweed pollen but clinically sensitive and not treated for house dust allergy exhibited symptoms in late September and only when heating systems were turned on, the symptoms ceasing, however, when the ragweed pollen is no longer in the air, proving the presence of both "allergens" to be necessary for clinical symptoms. It remains to be seen whether treatment with both ragweed pollen and house dust antigens will solve this problem. All symptoms which occur during the season cannot naïvely be ascribed either to the pollen or to failure of the type of treatment.

The results so far achieved have been described.[21-23] In every case, they

were better than the report. When, for example, a patient recorded symptoms during two weeks of house painting while on vacation during the pollen season, the pollen was considered as the cause and the result was termed a failure in treatment. In approximately half the number of patients in whom symptoms were noted, such extraneous causes could, at least, be strongly suspected.

In their present state, repository injections are probably not the final answer to the problem of treating pollinosis. They do represent a giant step forward to ever safer, easier, less expensive methods of freeing the patient from the tyranny of multiple injections to which the allergist, however bored, is also subjected.

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75 Bay State Road

A STUDY OF THE EFFECTIVENESS OF SUSTAINED-ACTION TABLETS

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THE desire of the medical profession for continuous therapeutic action at optimum dosage with fewer administrations has brought about the increased usage of sustained-action capsules and tablets. However, a thorough search of the literature failed to disclose any studies on the effectiveness of sustained-release tablets as opposed to tablets or capsules containing coated pellets. Most observations have been based on clinical results, either actual or expected, rather than on the disintegration of the tablet or capsule and the timed blood levels of the drug. Clinical response is undoubtedly important, but without laboratory evidence of absorption, one wonders how much of these compounds is actually utilized in dissolution.

The repeat-action tablet is, in principle, a double tablet, the core being similar to the coat in composition, with the two layers separated by a relatively resistant wall which prevents the disintegration of the inner portion until long after the outer has disappeared. The multiple-release capsule or tablet contains a myriad of medication-bearing pellets which have three or four times at which the pellets are released, depending on the thickness of resistant coatings applied to the pellets before they are mixed and packed in capsule or tablet form.

Unfortunately, the repeat-action tablet does not achieve a truly continuous release, but produces two dosage peaks with intervening periods of deficiency. While multiple-release capsules do better than repeat-action tablets from the standpoint of drug release, it is extremely difficult, if not impossible, to obtain uniformity of the coating material.

A new type of sustained-action tablet was made by imbedding crystals of the active drug in a matrix which was itself insoluble but subject to erosion in the gastrointestinal tract. As the surface of the drug-bearing matrix erodes continuously in the small bowel, minute increments of the drug are made available in a supposedly smooth, continuous process. Around this core of high molecular weight waxes and fats and their cache of active material, more conventional granulations are compressed to form an outer tablet which disintegrates very quickly, providing immediately accessible quantities of the drug.

The present study was undertaken to calibrate methods in assessing the

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claims made for these sustained-action tablets which the manufacturer has labeled Lontabs®.*

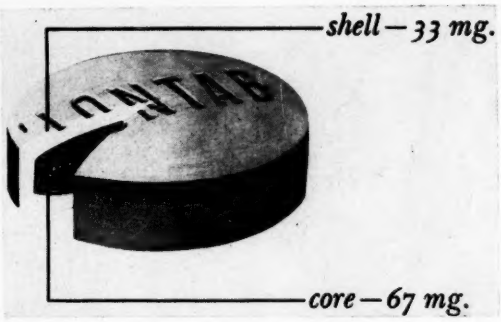

Fig. 1. Lontab® number 1.

METHOD

In order to visualize by x-ray just what happened to sustained-release tablets in the gastrointestinal tract, the Lontab® number 1 (see Fig. 1) was formulated with 100 mg sodium iodomethane sulfonate (Skiodan®) as the active ingredient in place of tripelennamine (Pyribenzamine®). This radio-opaque substance was preferred to barium, as it is soluble and is dissolved in artificial gastric and intestinal juices in approximately the same time as is tripelennamine. Due to the extraordinarily lengthy period necessary for partial release of the sodium iodomethane sulfonate as observed by x-ray, the manufacturer was requested to furnish a new formulation (Lontab® number 2), calibrated in artificial gastric and intestinal juices to complete release, if possible, in eight hours (Fig. 2).

It was planned to do serial tripelennamine blood levels on plain and sustained-release tablets; however, tripelennamine disappears from the blood stream so rapidly that it is not possible to do blood levels by conventional assay methods.[1] Urine levels were determined for tripelennamine at two, four, six, eight, twenty-two, and twenty-four hours by the method described by Perlman.[4] As only 10 per cent of the ingested tripelennamine is excreted in the urine and this over a period of eight to ten hours after a single dose, the results, at best, may be said to be equivocal.

Patients having had normal gastrointestinal x-rays were selected and given ten sustained-action tablets containing sodium iodomethane sulfonate which were swallowed after an eight-hour fast. Flat plate abdominal x-rays were taken at hourly intervals for the first twelve hours and then every four hours up to thirty-six hours after ingestion.

The clinical evaluation was made on allergic patients sensitive to ragweed, about half of whom had had specific hyposensitization treatment.

*The tablets used in this study were kindly supplied by Ciba Pharmaceutical Products, Inc., Summit, New Jersey.

The tripelennamine Lontab® number 1 and the tripelennamine Lontab® number 2, alike in appearance, were prescribed interchangeably for these patients twice daily in the treatment of hay fever symptoms. Response to

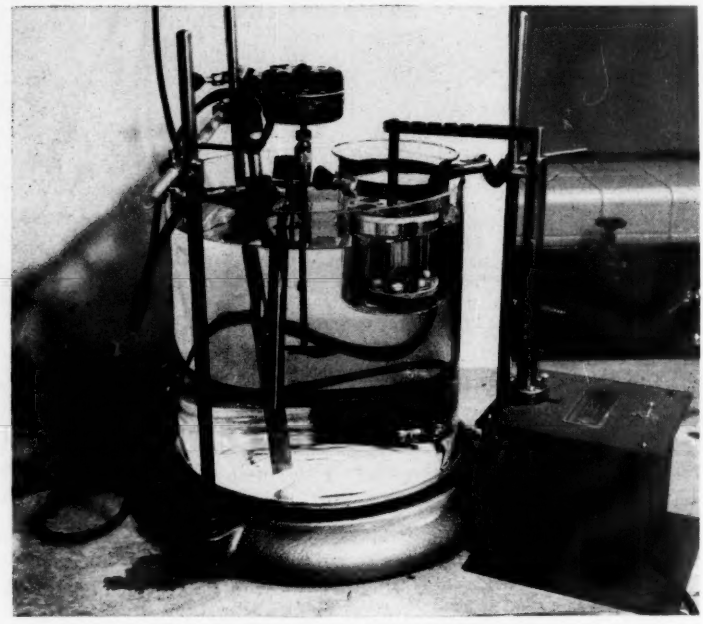

Fig. 2. Several Lontabs® are placed in the Disintegration Time Apparatus basket. The basket is raised and lowered for the first two hours in a beaker containing simulated gastric juice and for another ten hours in simulated intestinal juice. Evaluation is made by removing the solution from the basket each hour and the amount of contained tripelennamine or sodium iodomethane sulfonate is calculated in a 5 ml sample of the total solution. A fresh solution (artificial gastric or intestinal juice) is used each hour.

the tablets as noted by each patient was recorded by a disinterested technician who was not aware of which tablet had been used.

RESULTS

X-ray studies are graphically shown in Figures 3 and 4. Figure 3 (a-f) illustrates the action using sodium iodomethane sulfonate Lontabs® number 1. Figure 4 (a-d) depicts the sodium iodomethane sulfonate Lontabs® number 2. It is observed that some of the Lontabs® number 1 are still present at thirty hours and are estimated to be approximately 75 per cent dissolved. The Lontabs® number 2 show remnants at eight hours and no trace at ten hours.

The *in vitro* gastric and intestinal juice studies disclosed the percentage release of the entire dose at hourly intervals to be as shown in Figures 5a and 5b.

The hay fever patients were from twenty to sixty-five years of age, the

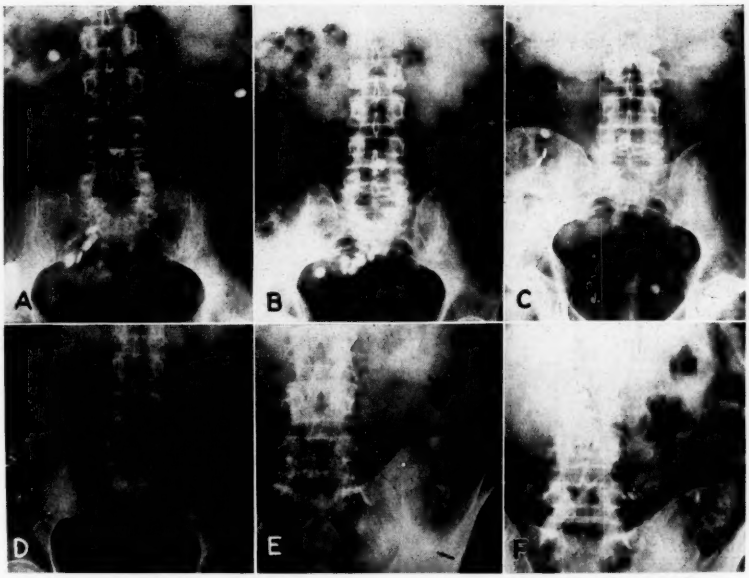

Fig. 3. (X-rays not retouched). Patient was given ten tablets each containing 100 mg. of sodium iodomethane sulfonate (Skiodan®) in the Lontab® formulation number 1. Radiographs show tablets in small bowel at two (*a*), four (*b*), six (*c*) hours and in ascending colon at eight and one-half (*d*) hours. At this time they are approximately 50 per cent dissolved. At twenty-six hours (*e*) the tablets are seen in the region of the left flexure and descending colon. At thirty hours (*f*) they are estimated to be 75 per cent dissolved. One appears to be dissolved to a lesser degree.

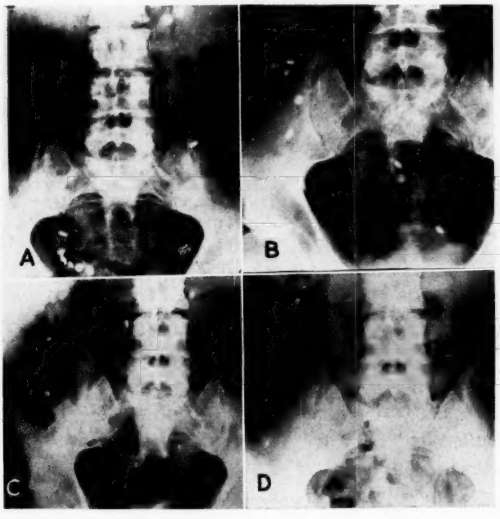

Fig. 4. (X-rays not retouched). Patient was given ten tablets each containing 100 mg of sodium iodomethane sulfonate (Skiodan® in Lontab® formulation number 2. Radiographs show tablets in stomach and small bowel at two hours *(a)*. At four hours *(b)*, six tablets are seen in the cecum and others in the ilium. At six hours *(c)*, there are three tablets in the transverse colon, others in the cecum. At eight hours *(d)*, remnants of the tablets are seen in the region of the colon. At ten hours, no trace of the tablets were seen.

median being forty-nine years. There were two females and thirteen males. Only eleven patients received both the number 1 and number 2

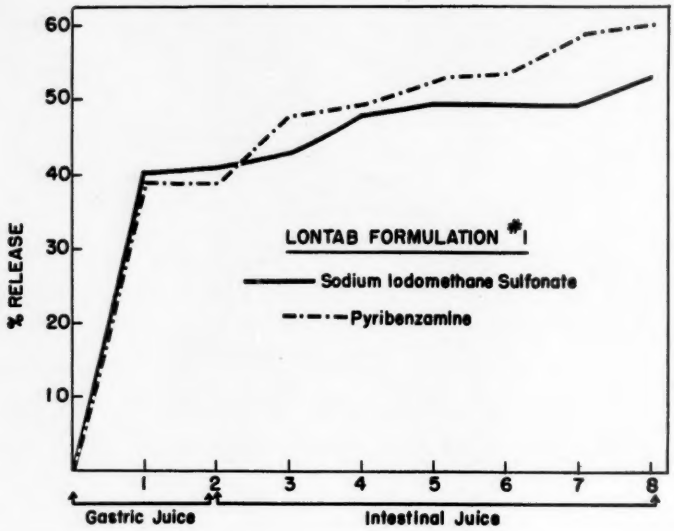

Fig. 5a. Lontab Number 1.

tripelennamine Lontabs®. The other four took only the number 2 Lontabs®. In grading the results, only three factors were considered: (1) Speed of onset of relief, (2) duration of relief, and (3) side reactions. An excellent result meant that all three factors were either better or as good as the compared tablet. Relief itself was not taken into account, since the same antihistaminic agent in the same dosage was used in both tablets. In this small series, formulation number 2 usually gave relief as fast or faster, lasted at least as long, with fewer side reactions (drowsiness), and was preferred by all patients (Table I).

DISCUSSION

In the past, x-ray studies of timed-disintegration capsules have been made, using barium in order to follow the dissolution of the capsule and contained pellets through the bowel. Disintegration is predicated on the formation of blobs or barium, which are usually so faint that they must be retouched to be identifiable. At this point, it is theorized by several authors that a soluble, active ingredient would be completely dissolved.[2,3] Using a soluble radio-opaque substance, such as sodium iodo-

methane sulfonate, which apparently has the same solubility as tripelennamine, is certainly easier and more accurate. The only contra-indication would be iodide sensitivity.

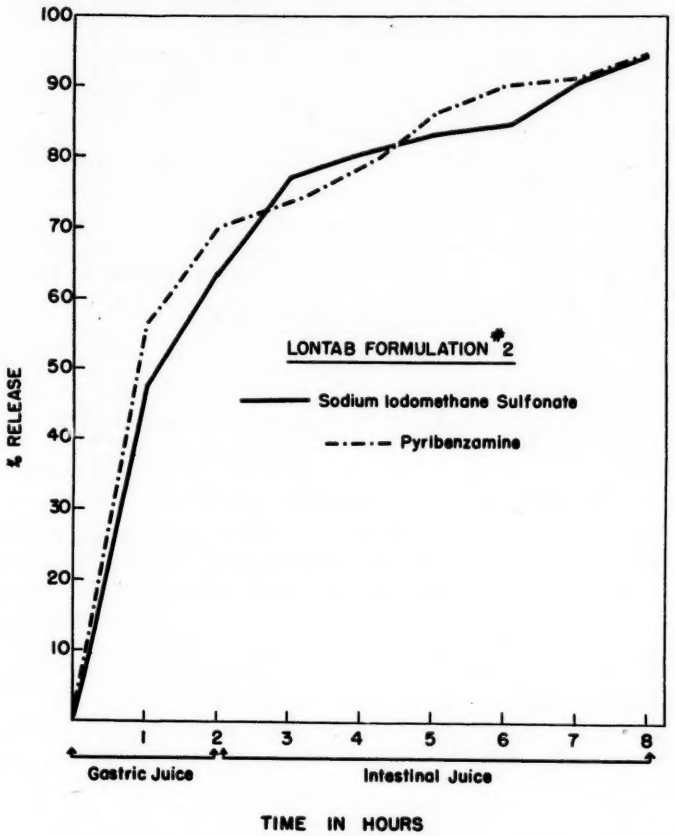

Fig. 5b. Lontab Number 2.

Although we were unable to correlate blood levels with x-ray studies, it would certainly be advisable and add strength to a study of this type.

Through the serial x-rays, *in vitro* studies and clinical results, tripelennamine is apparently available for absorption slowly, steadily and completely over the eight-to-ten-hour period after ingestion of the Lontab® number 2 tablet. By the same means, approximately 60 per cent of the medication in the Lontab® number 1 is available over the same interval.

Pyribenzamine Lontabs®, 100 mg, release rates are similar to those found with Lontabs® number 2.

If the amount of the drug used is effective, it can be assumed that continual, constant absorption is superior to intermittent dosage either by soluble tablets, capsules, or liquid or by repeat-action dosage forms.

TABLE I. RESULTS IN FIFTEEN HAY FEVER PATIENTS.

	Lontabs® Number 1		Lontabs® Number 2	
	No.	Per Cent	No.	Per Cent
Results				
Excellent	6	55	11	100
Good	2	18		
Fair	3	27		
Onset of action				
Faster			7	64
Slower	7	64		
Same	5	45	5	45
Duration of relief				
Longer			6	55
Shorter	6	55		
Same	5	45	5	45
Side reactions				
Yes	2*	18	0	
No	9	82	11	100
Patient preference	0	0	11	100

Four patients treated with Lontabs® number 2 did not receive other treatment for comparison. The results show:
Excellent 3 Fair 1 Reactions 1 (All reactions were drowsiness.)

SUMMARY

1. A new technique is presented for estimating dissolution of tablet or capsule medication by means of gastrointestinal x-rays.

2. The application of this technique, along with calibration in artificial gastric and intestinal juices, has demonstrated that *in vitro* and *in vivo* studies can and should be used by pharmaceutical manufacturers to make available dosage forms which will be absorbed in the time and amount desired by the prescribing physician.

3. Sustained-action tablets can be prepared so that constant, optimum dosage is made available to the patient over a period of eight to twelve hours.

ACKNOWLEDGMENT

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ATOPIC DERMATITIS: A REVIEW OF EIGHT YEARS

Part II

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THIS is the second paper reviewing our work with atopic dermatitis patients during the past eight years. The first paper* dealt with treatment results, both immediate and long-term. Here we evaluate various factors in the atopic dermatitis problem seen in a small-city and rural population. These factors are: (1) "nervousness" as the cause of the disease; (2) familial background; (3) duration of the disease (in relation to the patient's age when disease occurred); and (4) the value of skin testing and desensitization. This study was not preplanned; what is reported is what was observed in ordinary private practice.

Atopic dermatitis (also called generalized neurodermatitis, allergic eczema, infantile eczema (non-seborrheic), flexual eczema, exudative diathesis, and, in Europe, prurigo Besnier) is a disease manifested by an eczematous eruption of the antecubital and popliteal fossae, the volar aspects of the wrists, the face, as well as other parts of the body. The circumoral area is not usually involved. The eczema may be oozing, vesicular and crusting (especially in infancy) or dry, lichenified and scaling. Patients often have a personal or family history of other atopic allergic diseases such as asthma, hay fever, allergic sinusitis, allergic conjunctivitis, and in some cases, hives, migraine headache, and intestinal allergy.[7] The uncommon diseases, prurigo mitis and papular urticaria (when not due to insect-bite sensitization) are also labeled atopic. Atopic dermatitis does not include allergic contact-type dermatoses.

Fifty charts taken at random from our file on atopic dermatitis were completely reviewed. Questionnaires were sent out to 250 patients. The answers, plus the critical analysis of the fifty charts, are the basis for this report. The answers represented eighty-three patients. These, plus an additional twenty-three patients from whom the desired information was available, but the questionnaire not returned, totaled 106 patient studies.

A great deal of emphasis is placed on the nervous (i.e., psychogenic) etiology of atopic dermatitis. Lack of motherly love, poor home life, insecurity and repressed hostility have all been incriminated in the psychobiologic background of the disease. Williams[11] states that atopic der-

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*Presented by Dr. Hilliard M. Shair at the International Congress of Dermatology, Stockholm, Sweden, August 1, 1957.

matitis is associated with the child who has a characteristic temperament and a mother whose attitude toward the child is one of rejection. He feels that fathers play a passive and relatively unimportant role in the training and bringing up of children. Sulzberger and Zaidens[9] list atopic dermatitis as one of the skin diseases where emotion is a precipitating or perpetuating factor. Kierland and Walsh[2] feel that psychologic factors are one of the major trigger mechanisms in the disease. They discuss the role of emotional conflicts, sexual maladjustment, hatred, fear, guilt, masochism, exhibitionism and conflicts over masturbation. They state that there are unsatisfied dependency needs and suppressed hostility against a rejecting and dominating parent. Sternberg and Baldridge[6] found abnormal electro-encephalograms in nine of twelve cases of atopic dermatitis. They quote other authors relative to the finding of abnormal EEG's in patients with asthma. Russell,[5] of London, reported at the XI International Congress of Dermatology (1957) that patients with atopic dermatitis had twice the number of abnormal EEG's than the number found in a control group. At the same meeting Rush, Storkan, and Obermayer,[4] of Los Angeles, reported that rage precipitates a flare-up of "neurodermatitis" and conversely, improvement of the skin condition follows the release of tensions. It has been said that patients with atopic dermatitis have an obsessional-type psyche.

We have treated approximately 450 atopic dermatitis patients in the eight years being reviewed (1949-1956, inclusive), and despite the authorities quoted in the preceding paragraph, we are not particularly convinced that the psychogenic factors are major elements in atopic dermatitis.

There are, of course, psychosomatic aspects in every disease affecting human beings. The question here, however, is whether atopic dermatitis is essentially or predominantly a "nervous" affliction. It is a great temptation for the dermatologist to say, "Yes." This chronic, recurrent disease can wreck the emotional stability of a stout character. Allergic and dermatologic management is only partially successful. We have had no personal experience with the results of psychiatric therapy. However, despite the great temptation to blame the emotional makeup of the individual, we do not feel that atopic dermatitis patients need special psychological help. We will grant that associated with the young patient is often an anxious, distracted, and overprotective mother. We also observed that the adult patient is often quiet and shy. We admit emotional excitement increases the patient's itching and can cause the acute flare-up. Emotional upheavals act as trigger mechanisms but lack etiological importance. The personality of the patient is changed by the presence of his condition; it is not the cause of it. We rather think that these patients as a group do fairly well psychologically under trying conditions. Certainly they, as well as all medical patients, deserve the interest, comfort and tender-loving care that the physician can give them.

The word atopy (Coca and Sulzberger) implies a familial background

of one of the allergic diseases mentioned earlier. Baer[1] stated that 62 per cent of his atopic cases showed a familial history of atopy and 21 per cent had no familial history. Sulzberger and Wolf[8] mention that there is an abnormally high incidence of family history of allergy in patients with atopic dermatitis. Kurt Wiener[10] states that familial incidence is the most important factor in the known causes of atopic eczema. He mentions that 15 per cent of atopic dermatitis patients usually belong to families with other eczematous members. He quotes other writers as saying that the incidence of atopy (allergy in the family) ranges from 30 to 66 per cent. In 100 of our charts, the information in regard to familial atopic disease was as follows:

No information	11
No familial allergy	26
Familial allergy	63

Of those patients with a familial history, the father was atopic in 34.9 per cent (twenty-two), the mother in 36.9 per cent (twenty-three), and other members of the family, i.e., sisters, brothers, grandmothers, grandfathers, uncles, aunts), in forty-one patient histories.

Many patients with atopic dermatitis not only have a familial history of associated allergic stigmata but suffer from some of these themselves. No follow-up was obtainable for nine of the 106 cases. Twenty-seven of the cases had one of the associated allergies. Seventeen had two conditions and five had three or more.

Twenty patients had hay fever, twenty-five asthma, nineteen allergic rhinitis, one allergic conjunctivitis, nine allergic sinusitis, and fifty-one had no known atopic stigmata. These allergic conditions varied from slight to severe.

The case histories of eleven men and thirty-three women patients with atopic dermatitis are listed according to ages when the disease began. Twenty-two had the onset of their atopic eczema under the age of one year. Thirteen from one to five years of age, four from six to ten years of age, and three from eleven to twenty-one years of age. Two patients began their atopic eczema over the age of twenty-one years.

Of the patients who had their onset from infancy until five years of age (thirty-five), sixteen still had eczema by the age of ten, nine still had recurrences of the eruption in their teens, and three had eruptions as an adult.

Of the patients who had the onset in childhood, three still had the eruption in their teens and two still suffered from eczema as adults. In reviewing these charts, we found that of those patients who had the onset of atopic dermatitis in infancy (under one year of age) about 60 to 75 per cent had eczema in childhood, only half of these were bothered with the eruption in adolescence, and only a third of these had adult

eczema. Actually, there was less than 10 per cent of the whole group who had eczema as adults. Of those whose eczema occurred during the ages between six and ten, approximately one-third showed adolescent eczema. Most of these continued to have it as adults, approximately 25 per cent of the entire group. It is our impression that the earlier the age of onset of atopic dermatitis (as far as the skin eruption is concerned) the better the prognosis for freedom of eruption during future life.

In reviewing fifty charts, we found twelve patients who had received intracutaneous testings. Six of these were allergic to house dust, three to Alternaria, two to feathers, and the remainder had positive reactions to such things as cinnamon, caraway, wheat, wool, sweet corn, anise, rye, cotton seed, rabbit hair, cat hair, nuts, rice, cheese, ragweed, flax seed, thyme, dog hair, Hormodendrum, cow hair, goat hair, horse hair, camel hair, and silk. One patient with a marked hypersensitivity to house dust was started on a program of hyposensitization and soon afterwards the skin became markedly worse. Another patient who had a hypersensitivity to ragweed was desensitized orally. The skin remained unchanged but the asthma and hay fever symptoms disappeared. We do not routinely skin test our atopic dermatitis patients. If there is an associated hay fever or asthma indicating inhalant allergens, we feel it then necessary to determine, if we can, by intracutaneous testing what these particular allergens are. It is our impression also that hyposensitization to inhalant allergens is not the answer to the therapeutic success in atopic dermatitis. Milder[3] states that in his experience tests of ingestant and inhalant allergens are of little value in atopic dermatitis. It certainly is beneficial in some of the associated allergic stigmata. For the cutaneous manifestations of atopy, we still believe topical therapy is the treatment of choice. Oral or parenteral therapy is of help, and radiation whether it be grenz or x-ray is beneficial.

SUMMARY

The charts of 106 individuals, taken at random from our file of atopic dermatitis patients, were reviewed. Emotional disturbances were found to aggravate a pre-existing eruption but these individuals in most cases were not special psychiatric problems. Sixty-three cases had a definite familial history of atopy. Twenty patients also had hay fever, and twenty-five had asthma. Fifty-one patients had no known associated allergic stigmata. It was also found that the earlier the onset of the dermatitis, the better the prognosis for freedom of eruption in adult life. It is our belief that in the order of effectiveness, the best therapeutic measures for the cutaneous manifestation of atopic dermatitis are (a) topical medication, (b) radiation (grenz ray and x-ray), and (c) oral and parenteral medication. Hyposensitization is of limited value for the cutaneous eruption. The results of therapy were covered by one of us (HMS) at a presentation given in 1957 in Stockholm, Sweden.

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OF SCIENCE

"Science is not a photograph of the real world. It is a map, in which mountains, rivers, and valleys are variously coloured not to represent their actual tints, but because the colours can give us useful directions. It is one thing to say that a discipline can only rank as genuine science when it can also supply us with recipes for the practical conduct of affairs, and it is another to say that scientific research is and must always be confined to topics of immediate social value. If you have to build a railway you need a map. It is obviously superficial to draw a sharp distinction between the work done in mapping the actual track traversed as *useful* work in contradistinction to all the *useless* work of mapping the part of the territory over which no rails are laid down. One reason is that you cannot know what you will have to scrap till your task is finished. Another is that the existence of the railway may make it necessary or desirable to have a water supply, town, or sanatorium in the vicinity. What is easily overlooked is that the wells are tapped, and where no sanatorium is erected would not have been prospected *unless there had first been a definite social reason for constructing the map.*"—LANCELOT HOGBEN, *Science For The Citizen*, New York, Alfred A. Knopf, 1938.

THE INADEQUACY OF THE PASSIVE TRANSFER TEST AS A DIAGNOSTIC PROCEDURE IN PEDIATRIC ALLERGY

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IN 1921, it was found that when serum of an allergic individual was injected intradermally into the skin of a normal recipient and then the specific antigen was placed in the same site, an immediate wheal-type reaction could be produced. This has been known as the passive transfer test and the transferable antibody as the Prausnitz-Kustner antibody, named for its discoverers.[12] The phenomenon was confirmed by de Besche,[5] and has become widely accepted since.

Some allergists prefer passive transfer to direct intradermal testing in infants and young children since only a single venipuncture is required for the infant, and after proper preparation of the serum, all of the tests may be done on an adult. The advantage of convenience of the method is apparent, leaving only the question of its reliability.

The purpose of the present study was to evaluate the passive transfer test as a diagnostic procedure.

METHOD

In general, the original method of Prausnitz and Kustner[12] was followed. Blood was drawn from hypersensitive individuals. Since citrate has no effect upon antibody,[22] plasma from citrated blood was occasionally used. In other instances the blood was defibrinated. In most cases serum was obtained from clotted blood. All sera were sterilized by Seitz filtration. Normal individuals, called receptors, received 0.15 ml of serum intracutaneously, and twenty-four to forty-eight hours later were tested by scratch or intracutaneous method at the injected site.

The receptors were children ranging between eight and fourteen years of age. They abstained from the particular food against which they had been locally sensitized, since oral administration of these foods has been shown to give positive reactions which were so large that direct tests could not be done.[21]

RESULTS

There were sixty-eight receptors in all, fifty-eight of whom gave positive reactions at one time or another, while the ten who did not were eliminated from the results. Certain sera transferred to all receptors

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TABLE I. SERUM ANTIBODIES FROM AN INDIVIDUAL (J.P.) SENSITIVE TO SIX GRASS POLLENS WERE ALL TRANSFERRED TO ONE OR MORE RECEPTORS

Receptors	Allergic Antibodies					
	Orchard Grass	Redtop	Rye Grass	Sweet Vernal Grass	Timothy	June Grass
C	+	+	0	+	+	0
S	+	+	+	0	0	+
V	+	+	+	0	0	0
H	+	0	0	0	0	0

TABLE II. MULTIPLE SENSITIVE PATIENTS WITH ASTHMA SHOWING ALLERGIC ANTIBODIES TO SOME ALLERGENS AND NOT TO OTHERS

Case	Proved Sensitivity	Allergic Antibody	Number of Receptors	
			Positive	Negative
1. E. D.	Rabbit hair	Present	2	0
	Cat hair	Absent	0	2
2. A. H.	Cottonseed	Present	5	1
	Hazelnut	Absent	0	6
3. J. H.	Horse dander	Present	2	4
	Cat hair	Absent	0	5
4. H. A.	Cat hair	Present	3	0
	Mustard	Absent	0	3
	Egg	Absent	0	3
5. J. K.	Rabbit hair	Present	2	1
	Brazilnut	Absent	0	3
	Almond	Absent	0	3
	Blackberry	Absent	0	3
	Lentil	Absent	0	3
6. A. M.	Codfish	Present	3	0
	Mackerel	Absent	0	3
	Eggwhite	Absent	0	3
7. G. Q.	Eggwhite	Present	3	0
	Chicken	Absent	0	3
	Chicken feather	Absent	0	3
	Duck feather	Absent	0	3
8. N. DaC.	Eggwhite	Present	2	1
	Pea	Absent	0	3
	Horse dander	Absent	0	3
9. W. L.	Soybean	Present	3	0
	Horse dander	Present	3	0
	Rabbit hair	Absent	0	3
10. N. S.	Brazilnut	Present	3	0
	Butternut	Present	3	0
	Eggwhite	Absent	0	3
	Chicken feather	Absent	0	3
	Goose feather	Absent	0	3
	Duck feather	Absent	0	3
	Oat	Absent	0	3
	Almond	Absent	0	3
11. P. V.	Cottonseed	Present	27	0
	Eggwhite	Present	9	21
	Mustard	Present	2	12
	Kidney bean	Absent	0	11
	Potato	Absent	0	8

tested; others did not. For this reason and also because the antibody titer of serum varied, it was necessary to test several receptors before pronouncing a serum negative. Eighty-five per cent of the receptors reacted positively at some time or another.

TABLE III. MULTIPLE SENSITIVE PATIENTS WITH HAY FEVER SHOWING ALLERGIC ANTIBODIES TO SOME POLLENS AND NOT TO OTHERS

Case	Proved Sensitivity	Allergic Antibody	Number of Receptors	
			Positive	Negative
1. B. R.	Ragweed	Present	2	1
	Goldenglow	Absent	0	3
	Goldenrod	Absent	0	3
2. P. H.	Ragweed	Present	2	0
	Timothy	Absent	0	2
3. J. P.	June grass	Present	1	3
	Orchard grass	Present	4	0
	Redtop	Present	3	1
	Sweet vernal grass	Present	1	3
	Timothy	Present	1	3
	Rye grass	Present	2	2
	Ragweed	Absent	0	4
	Aster	Absent	0	4
	Cockleburr	Absent	0	4

To illustrate this point, in the case of the serum from a patient J.P. (Table I) sensitive to six grass pollens, orchard grass was transferred to all receptors, redtop to three, rye grass to two, sweet vernal grass, timothy and June grass to one each. Thus all six pollens to which the patient was sensitive by direct testing were not transferable to any single receptor, but a positive reaction was obtained to each pollen when transfers were made to several receptors.

The donors and receptors were tested for blood groups. Recipients from each group accepted antibodies from the opposing groups. Thus, the blood groups played no apparent role in the receptivity or transfer of Prausnitz-Kustner antibodies. This corroborates the findings of Smyth and Bain[18] and of Becker and Black.[2]

Allergic Patients Sensitive to More Than One Allergen Showing Antibodies to Some and Not to Others.—Eleven cases of allergic asthma in children with known dermal hypersensitivities were studied for the presence of Prausnitz-Kustner antibodies to determine whether sensitivities found on direct skin testing were all detectable by passive transfer (Tables II and III). The serum from those patients sensitive by direct testing to multiple allergens often showed passively transferable antibodies for some but not for all of them.

Serum from allergic patients showing Prausnitz-Kustner antibodies to a particular allergen in one recipient did not necessarily show it in another. When the titer was sufficiently high, all receptors gave positive reactions. When the titer was low, some receptors gave positive reactions while others did not.

Antibodies for cottonseed were demonstrable in practically all receptors. This may be due to the high antigenic potency of cottonseed or the component antibody-producing primary toxin—gossypol, which is present in practically all cottonseed preparations. We have also obtained a positive transfer to all recipients with peanut antibody.[16]

TABLE IV. MULTIPLE SENSITIVE PATIENTS WITH HAY FEVER SHOWING TEMPORAL RELATION OF THE PRESENCE OF PK ANTIBODIES AND THE TIME OF CONTACT WITH THE POLLEN

Case	Sensitivity	Time of bleeding in relation to previous pollination season	Time of bleeding in relation to pollen treatment	Antibody	Number of Receptors	
					Pos.	Neg.
C. S.	Ragweed	5½ months	During treatment	Present	2	0
B. R.	Ragweed	10 months	During treatment	Present	2	1
	Goldenglow	10 months	Untreated	Absent	0	3
	Goldenrod	10 months	Untreated	Absent	0	3
P. H.	Ragweed	9 months	During treatment	Present	2	0
	Timothy	11 months	Untreated	Absent	0	2
J. P.	Timothy	During pollination	Untreated	Present	12	0
	Rye grass	During pollination	Untreated	Present	12	0
	Ragweed	10 months	Untreated	Absent	0	12

TABLE V. SERA REACTING IN ALL RECEPTORS TESTED

Allergic Patient	Sensitivity	Number of Receptors
P. V.	Eggwhite	3
	Bean	3
	Cottonseed	22
G. Q.	Eggwhite	3
W. L.	Horse dander	3
	Soybean	3
N. S.	Brazilnut	3
	Butternut	3
E. S.	Horse dander	3
H. A.	Cat hair	3
A. M.	Codfish	3
H. D.	Lactalbumin	3
A. R.	Horse serum	4
J. P.	Orchard grass	4
M. L.	Lactalbumin	9
N. G.	Horse serum	16

In Table IV are listed four known cases of patients with hay fever, all reacting by direct testing to specific pollen antigens. In Case 1 (C.S.), the blood was drawn approximately five and one-half months after the pollinating season but this child had been injected with pollen extract a number of times before the blood was drawn. This may have stimulated the production of antibodies. In Case 2 (B.R.) the blood was drawn ten months after the weed pollination season and the Prausnitz-Kustner reaction to ragweed was present but not to goldenglow or goldenrod. This child was being treated with ragweed but not with goldenglow or goldenrod. In Case 3 (P.H.) the blood was drawn nine months after the ragweed season and eleven months after the timothy season and had Prausnitz-Kustner antibodies for ragweed and none for

TABLE VI. SERA REACTING IN SOME RECEPTORS, NOT IN OTHERS

Allergic Patient	Sensitivity	Serum Used*	Receptors	
			Positive	Negative
P. V.	Eggwhite	Bleeding 1	5	17
	Eggwhite	Bleeding 2	1	3
	Mustard	Bleeding 3	2	1
J. K.	Rabbit hair	Bleeding 1	2	1
B. R.	Ragweed	Bleeding 1	2	1
H. D.	Goat milk	Bleeding 1	1	2
E. T.	Horse dander	Bleeding 1	1	2
	Horse dander	Bleeding 2	1	2
J. P.	Rye grass	Bleeding 1	2	2
	Timothy	Bleeding 1	1	3
	Sweet vernal grass	Bleeding 1	1	3
	Redtop	Bleeding 1	3	1
	June grass	Bleeding 1	1	3
E. D.	Rabbit hair	Bleeding 1	2	3
A. H.	Cottonseed	Bleeding 1	5	1
J. H.	Horse dander	Bleeding 1	2	4
A. D.	Eggwhite	Bleeding 1	1	6
S. P.	Eggwhite	Bleeding 1	4	13

*Multiple sera from the same patient obtained from different bleedings are indicated numerically.

timothy. The presence of the ragweed antibodies here may well be due to the treatment this individual was getting at the time the blood was drawn. No treatment was being given for timothy. In Case 4 (J.P.), where the blood was drawn during the height of the pollination season for early grass, antibodies were present for timothy and rye grass. It was ten months after the ragweed season and no ragweed antibodies were present.

Varying Ability of Antibody-containing Serum to Sensitize Known Receptors.—In Table V are listed sera which were tested in known receptors and which produced reactions in all receptors tested.

On the other hand, in Table VI are listed a number of allergic sera which were tested in known receptors and which gave positive reactions in some and not in others.

No titrations were made of these sera but it appears from these results that the strength of the serum, as well as the individual receptor, varies.

Patients Showing Presence of Allergic Antibodies at Various Times.—In Table VII are listed several patients in whom the presence of antibodies could be demonstrated at certain times and not at others. Varying intervals elapsed but no study was made of the exact time when these antibodies were present or absent, except to indicate that the humoral allergic antibody is not a fixed substance which can be regularly demonstrated.

TABLE VII. SERA SHOWING THE PRESENCE OF ALLERGIC ANTIBODIES AT VARIOUS TIMES

Allergic Patient	Bleeding	Sensitivity	Allergic Antibody
A. H.	1st	Cottonseed	Present
	2nd (120 days later)	Cottonseed	Absent
J. H.	1st	Horse dander	Present
	2nd (38 days later)	Horse dander	Absent
P. V.	1st	Cottonseed	Present
		Eggwhite	Present
		Bean	Absent
		Mustard	Absent
	2nd (20 days later)	Eggwhite	Present
		Cottonseed	Present
		Bean	Absent
		Mustard	Absent
	3rd (14 days later)	Cottonseed	Present
		Eggwhite	Present
		Bean	Present
		Mustard	Present
	4th (77 days later)	Cottonseed	Present
		Eggwhite	Present
		Bean	Absent
		Mustard	Present
M. L.	1st	Lactalbumin	Present
	2nd (7 days later)	Lactalbumin	Present
	3rd (7 days later)	Lactalbumin	Present
E. S.	1st	Horse dander	Present
	2nd (20 days later)	Horse dander	Present
	3rd (30 days later)	Horse dander	Present
	4th (9 days later)	Horse dander	Present
	5th (1 year later)	Horse dander	Absent

In patient A. H., the presence of cottonseed antibody was found and 120 days later it was absent.

Patient J. H. showed the presence of antibodies to horse dander and these were absent from blood drawn thirty-eight days later.

In patient P. V., serum was tested for four antibodies: cottonseed, eggwhite, bean and mustard. At the first bleeding and the second (twenty days later) the presence of antibodies to cottonseed and eggwhite was demonstrated but not to bean and mustard. In the third bleeding (fourteen days later) antibodies were demonstrable to all four allergens. On the fourth bleeding (seventy-seven days later) antibodies were found to cottonseed, eggwhite and mustard, but not to bean.

In patient M. L., the presence of lactalbumin antibodies was found in serum at the initial bleeding and at two subsequent bleedings at seven-day intervals.

In patient E. S., the serum had demonstrable antibodies to horse dander at the initial bleeding, the second (twenty days later), the third (thirty days later) and the fourth (nine days later). These antibodies were absent from blood drawn about one year later.

COMMENT

Since Otto[11] and Friedemann[7] demonstrated that the blood of a sensitized animal could passively sensitize a normal animal, the antibody basis

for hypersensitiveness has been clearly established. When Prausnitz and Kustner[12] discovered that the allergic individual had in his blood an antibody which could be demonstrated by passive transfer to the site of a normal individual, they clearly indicated the importance of the receptor in these studies.

While some[8,9] have found that a small percentage of the receptors have non-reactive skin, others[13,18] believe that any receptor will give a positive Prausnitz-Kustner reaction if the serum antibody titer is high enough.

It is generally felt that once allergic antibody is present in the serum, it will be present indefinitely. The present studies clearly show this not to be the case.

Studies on serum sickness have demonstrated that Prausnitz-Kustner antibodies follow more or less the same curve of appearance and disappearance as precipitins and anaphylactic antibodies.[4,20] After the ingestion of new foods in early childhood, precipitins appear and remain in the circulation for a period of thirty to forty days.[17] It seems not unreasonable, therefore, to assume that Prausnitz-Kustner antibody acts in the same manner and remains in the blood for only a transitory period.

The assertion that the antibodies found in the allergic individual can regularly be transferred to a normal human receptor has not been sustained by the present data. This has long been indicated from animal studies. Prausnitz and Kustner were unsuccessful in attempts to passively transfer antibody from a fish-sensitive patient to guinea pigs. Others have demonstrated passive transfer of human serum antibody to guinea pigs[1,6,15,20] and monkeys,[8,19] but such transfers have not been uniformly successful.

We[14] attempted passive transfer to guinea pigs with thirty-two sera from eighteen patients who were sensitive to various proteins. Successful transfer was obtained with only fourteen sera from nine patients. Furthermore, sera drawn at different times from the same patient (as well as multiple tests on each serum) showed considerable variation in passive transferability to guinea pigs.

The present data have shown that Prausnitz-Kustner antibodies may not be detectable to all of the allergens to which a patient is sensitive. Moreover, Prausnitz-Kustner antibodies to an individual substance may not be demonstrated at all times in a single case. Variations in titer related to temporal factors are suggested by the hay fever cases which were studied. When blood was drawn during the grass-pollination season, Prausnitz-Kustner antibodies were found to tree and grass pollen, whereas no antibodies were present for ragweed eleven months after the previous contact. When a patient was being treated for ragweed, pollen antibodies were obtained, even though many months had elapsed since the preceding ragweed season.

While the present studies, as earlier ones, are inadequate for final

conclusions, it seems probable that a temporal factor exists but the exact time relationship requires further study.[10]

Levine and Coca[9] first suggested differences in titer of the antibodies. This was corroborated by later work. In certain instances in the present work antibodies were regularly transferred to all receptors while in others this was not the case. It is apparent that in order to be certain that antibodies are present, both multiple sera and several receptors must be used.

Thus, the Prausnitz-Kustner antibody has not been found as constant a criterion of allergy as the direct skin reaction in the hypersensitive individual. Indeed, based on the present data, the Prausnitz-Kustner reaction would seem to be an unreliable test and inadequate to establish the various sensitivities in a diagnostic study.

CONCLUSIONS

The Prausnitz-Kustner or allergic antibody is not found in the blood of allergic individuals at all times.

At a given time Prausnitz-Kustner antibodies may not be present for all of the allergens to which the individual is sensitive.

Not all persons are capable of successfully receiving passive transfer of serum known to contain antibody.

Not all receptors are passively sensitized with the same serum to equal degree.

These findings demonstrate that the passive transfer test, often used in determining the etiologic allergens in infants and young children, is unreliable and should be regarded as an inadequate diagnostic procedure.

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ANALYSIS AND SYNTHESIS

"In analysis, we start from what is required, we take it for granted, and we draw consequences from the consequences, till we reach a point that we can use as starting point in synthesis. For in analysis we assume what is required to be done as already done (what is sought as already found, what we have to prove as true). We inquire from what antecedent the desired result could be derived; then we inquire again what could be the antecedent of that antecedent, and so on, until passing from antecedent to antecedent, we come eventually upon something already known or admittedly true. This procedure we call analysis, or solution backwards, or regressive reasoning.

But in synthesis, reversing the process, we start from the point which we reached last of all in the analysis, from the thing already known or admittedly true. We derive from it what preceded it in the analysis, and go on making derivations until, retracing our steps, we finally succeed in arriving at what is required. This procedure we call synthesis, or constructive solution, or progressive reasoning.

Now analysis is of two kinds; the one is the analysis of the 'problems to prove' and aims at establishing true theorems; the other is the analysis of the 'problems to find' and aims at finding the unknown."—PAPPUS, *circa 300 A.D.*

DIAGNOSIS AND TREATMENT OF MENIERE'S DISEASE
Historical Report

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IN 1861, Prosper Ménière, a French physician who spent a great deal of time in a large hospital for the deaf in Paris, published some papers in which he pointed out that of a large group of patients with a diagnosis of "apoplectiform cerebral congestion," there were some who were different. These patients, he noticed, had sudden attacks of nausea, vomiting, rotatory vertigo, inability to walk. Most of the patients with apoplectiform cerebral congestion had similar symptoms. In addition, he found on careful questioning, that members of this group complained of difficulty in hearing in one ear and of a noise in the ear. He noticed on examining them during their attacks that they had nystagmus of the eyes. He watched many of these patients in the course of their disease and noticed that their attacks spontaneously went away in from four to twenty-four hours. Many of them had attacks again. He noticed that in between attacks these patients were perfectly well and healthy. Previously, Ménière had done a postmortem examination on a young girl who had died with what probably was leukemia, but who in her terminal illness had similar symptoms of vertigo, loss of hearing, noises in the ear and had nystagmus. At the postmortem examination, he noticed that the labyrinth of the inner ear on the side where she had hearing trouble was filled with blood. This was one of the earliest indications of the equilibrial functions of the inner ear. Ménière postulated in 1861 that these patients with the attacks described had disease in the inner ear rather than in the brain itself, and thus he was the first to delineate a disease occurring in the inner ear with predominantly equilibrial symptoms.

Since this description in 1861, the terms Ménière's disease and Ménière's syndrome or Ménière's symptom complex have come into common usage. There exists considerable confusion regarding these terms. Ménière accurately described a single condition without known etiology, with a very characteristic clinical pattern of recurring attacks, with periods of health in between, with normal otoscopic findings, and with certain abnormal hearing functions on the diseased side. The terms "symptom complex" and "syndrome" have been used to refer to conditions of dizziness or vertigo of every possible etiology, from a cerebral vascular accident and brain tumor to anemia, hypotension, head trauma, and purulent labyrinthitis to toxic effects of drugs on the labyrinth and brain. It is very

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important to distinguish between the syndrome and symptom complex and the disease. This may be done by means of a careful history and careful examination and tests. The history itself is the most significant factor because it is unique and is not easily confused with any other disease. In examination, normal otoscopic findings are the rule. The hearing loss, as found audiometrically, is usually what is called nerve type with equally reduced bone and air conduction, usually more pronounced in the lower tones. It is almost always unilateral although 5 per cent of cases of Ménière's disease are bilateral. Testing of the labyrinthine function by cold caloric testing usually reveals either a normal or slightly reduced function in the affected ear. The finding of a dead labyrinth on one side by caloric testing is usually presumptive evidence of some disorder other than Ménière's disease. More detailed audiometric testing, as loudness balance testing for recruitment, frequently reveals total recruitment in the affected ear in Ménière's disease which is almost the only disease producing this finding. Phonetically balanced word tests reveal very poor discrimination in Ménière's disease compared to other causes of deafness. The phenomenon of diplacusis, which is the subjective hearing of a higher or lower pitch in the affected ear, is frequently found in Ménière's disease. The results of fundoscopy and neurologic examination, except for the abnormalities of the eighth nerve function, are normal in Ménière's disease. With a careful review of the history and the examination and tests outlined it is almost always easily possible to make a definite diagnosis of Ménière's disease or to refute this diagnosis. It is emphasized again that it is important to make this differentiation because the treatment and the prognosis of Ménière's disease itself, as contrasted to the Ménière's syndrome and symptom complex, is vastly different.

The etiology of Ménière's disease is open to question. In 1938, Hallpike and co-workers in England demonstrated, by a postmortem examination, the hydrops or increased pressure of the endolymphatic duct in the cochlea and in the equilibrial labyrinth of the inner ear on the diseased side. This finding has been substantiated many times since. The present consensus is that the hydrops or increased pressure in the endolymphatic system is the result of an alteration in the arterial blood supply to the inner ear, probably the result of vascular spasm in the small arterioles of the inner ear itself. It is supposed that this may come about from neurogenic, hormonogenic and allergic causes. The medical treatment of Ménière's disease reflects the thinking regarding these etiologies.

In about 85 per cent of patients with true Ménière's disease, conservative or medical treatment will allow the patient to perform his usual occupation and his usual activities with a minimum of, or no disturbances. This does not mean that the disease is cured because the disease characteristically has remissions of varying and sometimes extremely long lengths, followed by recurrences of attacks. If this is carefully explained and

careful supervision and long term management is outlined, the previously noted results can be obtained. The measures used in this kind of therapeutic program include the following:

Vasodilators either by injection or by mouth or by both, for a considerable length of time;

The use of parasympatheticolytic drugs as banthine; the moderate restriction of salt intake; the avoidance of excesses of tobacco, alcohol, fatigue and tension.

The use during severe attacks of parenteral or oral antihistaminic agents such as dramamine.

The search for and treatment of specific inhalant or food allergies, which occasionally results in dramatic improvement and the occasional use of mild sedation and/or tranquilization.

Under long-term management of this kind with careful supervision and reassurance from the physician, most patients with Ménière's disease may be adequately controlled but, as mentioned, not cured. In about 15 per cent of cases, the disease either will not come under adequate control by these means, or because of occupational hazards or the extreme sudden severe falling type of spell which occasionally is the predominant symptom, other means are necessary to produce the desired results. In these instances, surgical treatment is justified if the disease is shown definitely to be unilateral. Surgical management at this time is best accomplished by ablation of the entire labyrinthine function on one side by either a trans-mastoid or trans-middle ear approach to the labyrinth and the avulsion of the endolymphatic duct. These are both safe and simple operations for a trained otologist and will produce complete loss of hearing and labyrinthine function without loss of cochlear function. It must be stated that most patients who are surgical candidates for this disease have extremely poor or useless hearing in the diseased ear. It must be emphasized that surgery should probably not play a part in the treatment of bilateral Ménière's disease. Streptomycin and sympathetic ganglion operations are still not controlled or widely used.

In summary, the diagnosis of Ménière's disease can be accurately made by the proper investigation of the history and the performance of certain definitive examinations and tests. The treatment of Ménières disease depends a great deal on the making of an accurate diagnosis. In the presence of true Ménière's disease, about 85 per cent of cases can be adequately controlled by medical means and the remainder can be controlled with proper surgical treatment. The most severe problem is the bilateral case which requires considerably more detailed and lengthy medical treatment in an attempt to obtain good control.

ALLERGIC RHINITIS ACQUIRED DURING THE PROCESSING OF EPOXY RESINS

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DERMATOSES from epoxy resins and their amine hardeners are common, but this is the first detailed report of allergic rhinitis acquired during their processing.

It is now twelve years since the initial development of the so-called "epoxy resins." Yet, despite the increasing numbers of skin rashes which have developed as a result of their present widespread usage, only three full-length articles have appeared to date in the American medical literature devoted to this subject.[1-3]

As has now been pointed out,[1-9] workers who handle the epoxy resins and their amine "hardeners" (particularly in the liquid state) during various processing stages are apt to develop an erythematous eczematous dermatitis on the central third of the face, the nose, and the adjacent portions of the cheeks, the upper lip, and the eyelids, as well as on the hands and forearms.

The purpose of this article is to draw attention to another less obvious condition that may be acquired during the processing of these resins: allergic rhinitis due to the inhalation of their fumes. Hine *et al*[3] in their thorough study recently published, stated that "potting operations were found occasionally to give rise to noxious, although not toxic, fumes," and they made short, passing reference to a complaint of irritation of the upper respiratory tract.

It is not my present intention to discuss the chemical, dermatologic and toxicologic aspects of the epoxy resins, inasmuch as the above-cited papers have covered them in fairly good detail. However, I do believe I should point out the extent to which the epoxy (ethoxylene) resins are now appearing in widely different types of industries. They are being used as surface coatings, adhesives, molding compounds, for casting and encapsulation purposes, as laminates and prosthetics; they are being used to reinforce other plastics, and also make other plastic tools and dies.[2]

CASE REPORT

The case presented herewith is that of a woman, white, forty-nine years of age, who had worked mixing and pouring epoxy resins over a period of eight months. She had been treated by her local practitioner for what she thought was sinus trouble, characterized mainly by running nose and frequent sneezing during the day (especially while weighing the chemicals in her plant), and nasal obstruction with the sense of impending suffocation while in bed at night. Upon referral to a nose

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specialist, results of x-rays of her sinuses were negative, and the specialist made a diagnosis of rhinitis due to the inhalation of fumes at work.

Since she had also suffered from a dermatitis of her hands of six months' duration, she was sent to my office for treatment of that condition. Upon examination, the dorsum of the left hand, over the first knuckle and the skin adjacent to it, showed pinkness and vesicles in an area approximately 1½ in. x ¾ in. Diagnosis of contact dermatitis from epoxy resins was made. She was one of four patients from the same plant being treated for contact dermatitis.

On her fourth visit, the patient asked me if there could be any significance in the fact that for some months she felt as though she had been "smelling ammonia" while at home at night, or even while visiting friends in their homes. She had been assured that there was no ammonia present in the various places where she thought she had detected the odor. The amine hardener which she brought in had an odor similar to that of ammonia, which indicated that the inhalation of organic amines while at work had irritated the nasal passages, causing this later sensation of "smelling ammonia." The diagnosis of the nasal specialist was thereby substantiated, particularly since it was established that, upon mixing the hardener and the epoxides, the resultant heat evolved would cause the fumes to be dispersed into the air and inhaled by nearby workers. The patient stated that she and a co-worker had become known as the "sneeze twins," but that the other worker was reluctant to report her condition to the management, lest it affect her job status.

The patient was removed from all contact with epoxy resins for a period of one month. On her final visit, her dermatosis was cleared, and she said that her nasal condition had improved so much that she could sleep without the feeling that she was going to suffocate. She stated that she did not sneeze nearly as much as she had previously, and that her nose specialist told her that the irritation had subsided remarkably. At the time of her last visit to my office, a container of amine was held close to the patient's nose; she breathed the fumes, and sneezing immediately followed, then running of the nose, and then a "stuffed" nose. This exposure was carried out in order to prove the cause of her rhinitis.

SUMMARY

A case of allergic rhinitis from inhaling epoxy resins and their amine hardeners during their processing state is reported in detail for the first time. Dermatoses resulting from these products are common.

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Progress in Allergy

DERMATOLOGIC ALLERGY V

Critique and Review of the Recent Literature

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A REVIEW of the current literature as it relates to dermatologic allergy is again presented. Articles of interest have been abstracted from current journals, and abstracts in various periodicals were also a fruitful source of information. The *Yearbook of Dermatology and Syphilology* as well as the *Review of Allergy and Applied Immunology* are both examples of rewarding reading for allergists who are confronted with problems of dermatologic allergy in everyday practice.*

Advances in therapy with the newer steroids triamcinolone (Aristocort® and Kenacort) and methylprednisolone (Medrol) appear this year. Immunologists, hematologists and workers in the basic sciences are clarifying our concepts of allergic vasculitis (angiitis). Studies dealing with heterologous tissue graft acceptance are bound to disclose further basic concepts in immunology. Publicity of drug reactions has borne fruit. Judging by current reports, fewer deaths have resulted this year from anaphylactic reactions to penicillin. Studies of cutaneous granulomas and extensive reviews of what is new in poison ivy dermatitis have appeared. These, together with expansion in many other facets of our knowledge of dermatologic allergy, attest to a continued lively interest in our specialty.

The review is divided for convenience into the following subsections: (1) allergic eczematous contact dermatitis; (2) atopic dermatitis; (3) urticaria and angioneurotic edema; (4) drug allergy; (5) steroid hormones, and (6) miscellaneous allergies.

ALLERGIC ECZEMATOUS CONTACT DERMATITIS

Experimental Studies.—Epstein and Kligman[72] were able to transfer allergic contact-type delayed sensitivity in man. Patch tests were made by placing the test substance in acetone in a round cup on the skin of the forearm. A stream of air evaporated the acetone, leaving the test material as a fine crystalline deposit on the skin. Three contact allergens—pentadecyl catechol (P.D.C.), 2, 4-dinitrochlorobenzene (D.N.C.B.), and paranitrosodimethylaniline (N.D.M.A.)—were used. Transfer materials were obtained from bullae induced by the allergen, by cantharidin, or by a combination of both. In addition, leukocytes were obtained from whole blood. Pentadecyl catechol was readily transferred in seventeen out of nineteen

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This review will appear in two parts. The second half, to appear in the March-April issue, will include the complete list of references.

*An abridgement of this review will be published in *Review of Allergy and Applied Immunology.*

cases with blister fluid as well as with peripheral blood leukocytes. D.N.C.B. and N.D.M.A. sensitivity could be transferred in five out of thirteen cases. It was also found that transfer sensitivity occurred with cell-free blister fluid, suggesting the presence of free antibodies. Conventional antibodies are located principally in the gamma globulin fraction of serum, but allergic contact dermatitis can develop in patients with agammaglobulinemia.

Baer[9] discussed the prevention of allergic sensitization. It is noted that most studies in the field of allergy have dealt with finding the etiologic factors and with various forms of allergic reactions and the mechanisms by which they are produced. Methods for demonstrating allergic changes and procedures designed to diminish or abolish already established allergic hypersensitivity have also been investigated. It has previously been shown that the development of allergic sensitization to neoarsphenamine in guinea pigs could be specifically inhibited by an intracardial injection one day after a potentially sensitizing dose of neoarsphenamine had been injected into the skin. Animals prefed with picryl chloride had a significantly diminished susceptibility to cutaneous sensitization. In man, subsensitizing doses of dinitrochlorobenzene prior to sensitization did not diminish sensitizability. Ordinarily, heterologous skin grafts do not survive. However, if a suspension of cellular material from mice is injected into pregnant mice, a graft from donors of the cellular material becomes acceptable. This is a specific experiment. Prefeeding of pregnant guinea pigs with picryl chloride and dinitrochlorobenzene did not prevent sensitization of the offspring to these agents, but capacity to undergo sensitization was reduced—a seemingly specific effect. Some experimental evidence in animals has also shown that exposure to allergens after birth, that is, during the first few days and perhaps weeks of life, produces some degree of tolerance to that allergen for a period of time. In studies on humans, some instruct pregnant women to avoid eggs and cheese and to take only one pint of milk per day, boiled for ten minutes, to reduce allergenicity. In addition, it has been shown that of ninety-six infants who did not receive cows' milk very early in life, only 8 per cent developed atopic dermatitis compared with 30 per cent in a control group of sixty-five siblings. Furthermore, the incidence of allergic asthma and rhinitis was much greater in the children who had been fed cow's milk very early in life.

Roberts and Dixon[210] immunized rabbits with bovine serum albumin and others with bovine gamma globulin. After a suitable interval, the lymph node cells of these rabbits were transferred to x-radiated recipient rabbits. These were then challenged with homologous antigen labeled with I^{131}. It was found that the total specific antibody synthesized by the transferred cells during the first eight days amounted to approximately two-thirds of the wet weight of the transferred cells. However, observations made with the nonsoluble, bacillary antigens showed no antibody production when lymph nodes were incubated with the soluble antigens used in the present study and washed before injection into recipients.

Acanthosis of the guinea pig nipple was produced by the application of estrogen, and acanthosis of skin of the flank by the use of a mixture of cetyl and propyl alcohols.[60] Epidermal thickening thus produced protects to a certain degree against primary irritants and sensitizing substances such as chrysarobin and dinitrochlorophenol, respectively.

Rostenberg[215] discussed a report by Derbes and Caro,[57] "Localized Eczema Induced by House Dust Extract Injections." It is Rostenberg's opinion that eczema produced by house dust injections arose because of the concomitant development of an eczematous type of delayed hypersensitivity

to an ingredient in the house dust antigen. The development of a dermatitis from the extracutaneous introduction of antigens to which a person is eczematously sensitive is a well-known clinical occurrence—being noted, for example, after injections of salvarsan, sulfonamides, and so forth. If localized eczematoid reactions are explained on the basis of local conjugation, they cannot be attributed to atopic antibodies which are freely diffusible substances. Derbes[55] stated that this same phenomenon has been seen in patients receiving grass or ragweed extract. Results of a patch test to dust were negative in the case under discussion.

Baer and others[11] studied the allergic eczema-like reaction and the primary irritant reaction in the acanthotic skin of the guinea pig. Since it is impossible to observe histopathologic events in the human skin with successive biopsies, it was decided to study the skin of guinea pigs which can be made acanthotic and would serve as a useful laboratory tool. The acanthosis on the flanks of guinea pigs was produced by applications of squalene and this was followed by the gradual evolution of an eczema-like reaction to 2, 4-dinitrochlorobenzene. This was then compared to the skin reactions from a primary irritant with vesicant properties such as cantharides tincture. The allergic eczema-like reaction develops slowly and gradually, the first changes becoming visible in the upper cutis at about the fifth to sixth hour. The subsequent changes were disturbances of the basal-cell margin followed by intercellular edema, spongiosis and vesiculation, most pronounced in the midportion of the rete. The reaction to the primary irritant, on the other hand, was rapid and profound. Severe damage was visible after one hour, and was characterized by damage to the parenchyma with acantholysis and damage to the cytoplasm and nucleus including intranuclear destruction of chromatin. Evidence of eczema-like spongiosis was entirely lacking. In the discussion of this paper, Pillsbury[163] presented the work of Epstein and Kligman with serial biopsy studies made on prisoner subjects, developing allergic contact dermatitis at one, two, three, four and eight hours on the same individuals. The earliest histologic changes, at one hour, are edema about the capillaries with subsequent perivascular collections of round cells and small lymphocytes. At four hours, the most sensitive subjects should show a cellular infiltrate; edema in the upper dermis is striking, and the epidermal changes seem secondary to this. Using 0.1 per cent of cantharidin in acetone on the intact skin, a histologic section was made in ten minutes. The section showed acantholysis as the primary irritant action of cantharidin. In further discussion, Rostenberg emphasized that the allergic eczematous reaction appears more slowly than the primary irritant reaction. It is generally believed that sensitization to a simple chemical is accomplished by means of a conjugate formed between the allergen and some body constituent, possibly protein. Most workers, on purely chemical grounds, believe it to be the epidermis, and Eisen has provided some immunochemical evidence to support this view. Rostenberg's personal theory is that as a result of such a conjugation, an enzymatic adaption takes place, probably in certain cells of the reticuloendothelial system, which adaptation is passed on to the descendants of these cells. In the nonsensitized animal, the cells which escape through damaged blood vessels do not have an adapted enzyme system; hence, the reaction dies of inertia. In the previously sensitized animal, however, some of the cells which escape have an enzyme system specifically adapted to react with the conjugated antigen formed in the general area of their escape; therefore, the inflammatory response is perpetuated and intensified. In the case of strong irritants, such as mustard

gas and lewisite, direct biochemical evidence has shown that there is direct interference with enzyme systems such as hexokinase and pyruvate oxidase. Hence the reaction would take place more quickly.

Sidi and others[233] found eight patients who were sensitive to both neomycin and streptomycin. The type of reaction after topical sensitization to antibiotics seems to be somewhat different from that expected in the usual allergic contact dermatitis. Instead of an acute vesicular oozing process at the site of contact, the reaction is more often of the dry, desquamative, spreading type which may, at times, involve covered areas, more suggestive of atopic dermatitis. Because of the widespread use of neomycin, it was hoped that further studies along these lines would reveal more data on cross-sensitization between neomycin and streptomycin. In discussion, Livingood[134] stated that for some time he had observed hypersensitivity to neomycin, as has Epstein. When the antibiotic was omitted and hydrocortisone used alone, the eczematous process cleared in some cases. Peck,[161] likewise in discussion, raised a number of questions in this connection. He wondered what the relationship was between an intradermal test with penicillin in a patient sensitive to penicillin and a patch test with the same material. There still is no explanation why a patient with T. purpureum infection may show only an immediate reaction to trichophytin, while the same antigen is present to give a delayed reaction in a patient with trichophytids. Baer[8] stated in discussion that while neomycin at first seemed to be the preferable antibiotic for local application, compounds of the tetracycline group have a very low eczematogenic sensitizing capacity and their topical use has not interfered to any significant extent with their systemic administration. Mayer,[142] in discussion of cross-sensitization, stated that the question arises as to why, within groups of closely related and cross-reacting substances, certain compounds are strong, others are only weak sensitizers, and others only elicitors. This may be the result of differences in exposures, differences in the mode of application, differences in solubility, rapidity of elimination, chemical stability, and so forth. All cross-reacting compounds of low molecular weight are haptens which acquire sensitizing properties only after they have been attached to a suitable carrier to form antigenic substances of high molecular weight. It is generally assumed that the carriers to which haptens become attached do not play any active role in the process of sensitization. Mayer, however, believes that the type of sensitization seems very much dependent upon the chemical and physical nature of the carrier (globular or fibroid protein, ground substance or lipopolysaccharides). This may explain dermal as well as epidermal sensitization since the hapten will combine upon epidermal application with keratinic and collagenic substances, while in the dermis one deals with ground substances and globular protein. The compensability of patients who suffer contact dermatitis caused by rarely observed antigens such as streptomycin and neomycin cross-sensitization, was discussed by Derbes.[56] The law states, and many cases come to trial before commissions, that if a substance causes sensitivity only rarely, liability cannot be charged to the manufacturer or seller of that commodity. Thus, in the case of Frankes v. Bennett (146, S.W. 2d. 163 Arkansas) it has been ruled that "it is common knowledge that many people are allergic to particular foods and cannot eat them no matter how pure nor how well prepared." Other decisions, for example, Barrett v. Kresge (19A, 2d. 502, 144 Pa. Super. 516) ruled that the dermatitis which a buyer suffered from wearing a dress resulted from her individual allergic nature, instead of from the character of the dye, and that the dye in the dress would not

have harmed a normal person. The seller of that dress was not liable under the Sales Act relating to implied warranty of fitness. In Kroger v. Industrial Commission (Wis. Supreme Ct. decided 1/13/42) the appellant contended that the law was not intended to cover every allergic tendency of certain sensitized individuals to certain substances. The reviewer notes that in spite of these decisions, the compensability laws of the various states differ considerably.

Gaul[92] investigated the complaint of many persons who have a tendency to suffer from skin irritations under and around their rings. Hot weather, with associated sweating, is an important factor in the production of such irritation. In addition, other kinds of jewelry including metal ornaments, fasteners, and pins are just as likely to cause irritations. A number of studies were made for possible accessory factors related to this irritation of the skin by jewelry. Copper and copper alloy in silver have been shown to corrode readily on the skin and, in the presence of an adequate concentration of salt, a primary irritant is produced. It appears that thermal and psychic sweating can deliver to the skin surface sufficient amounts of sodium and chloride ions which, when concentrated by evaporation, reach a saturation point and readily attack metal.

Clinical Aspects.—The epoxy resins were introduced in 1946 and are finding increasing use in industry, according to Morris.[148] They have a wide range of viscosity, from low-viscosity liquids to high-melting-point solids. The curing agents may also be liquids or solids. The fillers employed are usually solids and the solvents are usually liquids. These agents are used in industry as surface coatings, adhesives, molding compounds, for casting and encapsulation purposes, in the tool and dye industry, in laminating and in reinforced epoxy-plastics, and in alloys with other materials. The chemistry of the epoxy resins is discussed as well as the use of curing agents and the sensitization that may occur as a result of their use in industry. Clinically, patients presenting dermatitis from epoxy resins usually show eyelid involvement. The hands and various portions of the face are the next most frequently affected areas. Workers should be instructed as to the hazards involved in handling these epoxy compounds.

In Great Britain, the epoxy resins which are being widely used as adhesives and casting resins are called "epon" or "araldite."[97] Because of the possibility of sensitization with this new industrial agent, workers should be trained in the use of these resins by experienced men and should be told that traces of the casting resin on tables, chairs, shoes, clothes, machines, buttons, door handles, pencils, and so forth, may be the source of skin inflammation. When apparatus is cleaned with solvents, the worker should wear gloves of polythene. Ketonic solvents are preferable. General hygienic care should extend to washing facilities, pre-employment medical examination and strict observance of personal hygiene habits for each worker, in order to prevent sensitization.

Gaul[91] reported an instance of glue dermatitis attributed to epoxy resin. These agents may sensitize, if not thoroughly heat cured. Heat alters the structure of the resins sufficiently to render the sensitizing group innocuous. The epoxy resins are noted for their superior mechanical, electrical, chemical and weathering characteristics. They have satisfactory adhesive properties for metal and ceramic fabrication which has led to their extensive use in the manufacture of transistors, capacitors, rotors, stators for small motors, commutators, glass laminates, bonding, vacuum forming molds, drill and checking fixtures and jigs, and matched molds for

laminating. They are widely used for castings and in the apparatus, plastic, electrical, automobile, lacquer, paint and aircraft industries. The resins (ethoxyline or epoxide resins) are offered under the trademarks of "epon" or "araldite." In other studies it had been found that skin irritations were caused by contact with the resin, the hardener, or mixtures of these two components in the liquid stage before setting. The set, hardened resin appeared to be innocuous.

Kligman[125] has presented a fundamental review of our knowledge of poison ivy dermatitis, together with many additional observations based on an extensive clinical investigation. The family Anacardiaceae includes a number of immunicologically related plants which are dermatitogenic. The two most important are Rhus radicans (poison ivy) and Rhus toxicodendron (poison oak). The four Rhus allergens have the common chemical skeleton of a catechol with a 15 carbon side-chain in the 3 position. The chemical requirements for strong cross-reactivity are the presence of free phenolic groups and a long side-chain in the 3 position. The allergenic principle is present in all parts of the plant which contain resin canals. Its release requires bruising of the tissue. All persons can become Rhus-sensitive with sufficient exposure. There is no evidence of spontaneously acquired immunity, or of racial immunity. About 50 per cent of young adults will react positively to the application of bruised leaves. The incidence is lower in the darkly pigmented races. Sensitivity gradually declines with age. Once lost, sensitivity is not easily re-established. Sensitization cannot be prevented by prior feeding or contact with the allergen. The degree of sensitization is revealed by quantitative patch tests with serial dilutions. Following severe widespread Rhus dermatitis, the skin may show two opposite types of reactions: supersensitivity or hyposensitivity. Unusual complications of Rhus dermatitis include eosinophilia, kidney damage, urticaria and dyshidrosis. No practical topical measure will adequately protect against field exposures to Rhus plants. Various agents including soap and water washing, barrier creams, and detoxicants were used without effect. No topical therapy is efficacious in aborting or moderating Rhus dermatitis. Nonspecific dermatologic measures are helpful, and systemic corticosteroids do benefit Rhus dermatitis. Injection of Rhus antigen should not be made during an acute attack of Rhus dermatitis. This article is highly recommended by the reviewer for detailed reading in the original for all physicians who are called upon to treat this disorder.

Brodey[26] described a fifty-one-year-old carpenter with an extremely pruritic eruption. There were periods of remission, and exacerbations occurred mostly in the summertime. Results of patch tests with the oleoresin of short ragweed and with pyrethrum powder were strongly positive. Patch tests with turpentine, 50 per cent in olive oil and with chrysanthemum leaf gave negative results. The patient improved after treatment with corticosteroids, antihistaminics and superficial low-voltage unfiltered x-rays. The finding of ragweed dermatitis is relatively uncommon in consulting practice in New York City. The reviewer adds that he has diagnosed and treated about fifty such patients from the New England area in the past ten years (*J. Allergy*, 1953). This dermatitis is not uncommon in the Midwest.

Since the introduction of tropical timber for use in various industries, cases of skin damage have been reported on many occasions. Schulz[224] examined three carpenters in whom dermatitis developed eight to ten days after they had worked with iroko, an African wood similar to teak. Skin

tests showed positive patch reactions with iroko, but not with teak. Results of tests with 1 per cent chlorophorin—a phenolic resin first isolated from iroko in 1949—were also strongly positive. Chlorophorin is chemically related to toxicodendron (poison ivy) and cardol obtained from the Japanese lacquer tree.

Reports of allergy to tobacco are rare. Shanon and Tas[227] reported the case of a healthy seventy-two-year-old individual who developed a dermatitis of the nose after using sniff tobacco. Patch tests with tobacco gave positive results. Control studies were also made. It was concluded that the tobacco and not the additives had caused the localized dermatitis in the region of the external nares in this patient.

Wright and Tschan[266] observed that cashew nut dermatitis is extremely rare in the United States since the tree grows chiefly in tropical America, Africa and the West Indies. A sixty-year-old woman who gathered raw cashew nuts in the shell while traveling in Ceylon is described. That evening severe inflammatory dermatitis of the hands, with scattered areas of inflammation on the face and neck developed. Some time later, on her return to the United States and while cleaning out one of her bags, she found twelve nuts which she opened to show to her family. Within two hours a burning sensation of the face, hands and neck developed, and by the following morning all of these areas were severely inflamed and swollen.

Cipollaro[41] recorded the case of a forty-one-year-old woman in whom an eruption involving the hands and forearms developed. The eruption was diagnosed as poison ivy rash. Later the eyelids became edematous and erythematous, and the eruption persisted. Patch tests to a number of agents, including Thermofax paper, were then made. This paper gave a four plus eczematized reaction. The patient dates her eruption from the time of acquisition of the Thermofax copying machine in her office.

A recently introduced office procedure for duplicating the printed word involves use of the Thermofax process which requires a particular type of paper subject to heat, light and pressure while in close contact with the page which is being duplicated. After exposure for a few seconds, a direct positive image is obtained and the copy may be used immediately. Hasegawa and others[105] describe two patients in whom contact dermatitis developed following the use of Thermofax copy papers. Patch tests in both patients were made with the pre-processing and post-processing copy paper. Positive test reactions to Thermofax paper were obtained in both cases.

Kendrick[120] reported six office workers employed in the billing department of a large corporation. These men suffered from a rather severe dermatitis which had been proved to be caused by Thermofax paper. This was in the short period of about six months between October 1956 and February 1957. In April 1957, all the Thermofax copying paper on hand was exchanged for a new type which, on patch testing, proved negative in these patients. It has been learned that the antigen in the old Thermofax paper was tertiary butyl catechol.

Sheard and others[229] reported five cases of an unusual type of contact dermatitis of the face and hands in office workers. This condition is caused by high-speed-duplicator papers. Substitution with a new hypoallergenic paper (J-1 and J-10) enabled one patient to continue work.

An eruption which developed in a middle-aged office worker proved to be the result of contact with Thermofax paper.[234]

Fisher[76] described a fifty-year-old woman with contact dermatitis resulting from Thermofax paper.

In the dermatologic review of 1958, the work of Stephan Epstein and his studies of dermal contact dermatitis resulting from neomycin were reviewed. Forty cases of proven contact sensitivity to neomycin are reported and while contact dermatitis from this agent is considered rare, it apparently often goes unrecognized. The clinical appearance in many instances is that of an aggravation of a pre-existing dermatitis and not the obvious picture of an acute contact dermatitis. Even in the sensitive individual, the combined use of neomycin and hydrocortisone may appear to be of temporary benefit. Patch tests with preparations containing neomycin, and even a 10 per cent neomycin solution may give negative results. When it is positive, the reaction consists of a papular eruption, not the usual vesicular lesion. Intradermal tests with 1:1000 dilutions of neomycin are usually positive and those with 1:100 dilutions apparently are always positive. It is to be noted that the reaction occurs as a delayed tuberculin-type papule which appears after twenty-four to forty-eight hours and persists for one to several weeks. Neomycin remains a valuable topical antibiotic which can be used with comparative safety, provided one is aware that sensitivity of this drug is not as rare as is generally thought. The concept of dermal and epidermal sensitivity in contact dermatitis is discussed.[67] Dermal-delayed sensitivity to nickel and chromate had previously been described by Epstein. Theoretically, at least, there are two forms of contact dermatitis—one in which the epidermis is the main shock organ (epidermitis) and the other in which the dermis is the chief organ of reaction (dermitis). In contact dermatitis, the allergen is not a complete antigen. In order to become one, it must combine with some of the body's proteins. It seems likely that the combination differs, depending upon the site of sensitization. If the combination is with proteins of the epidermis, then epidermal contact dermitis is present—manifested clinically by a vesicular dermatitis and microscopically by spongiosis and intra-epidermal vesicles. Other chemicals apparently attack proteins of the dermis and a papular dermatitis may appear with a different type of microscopic picture. It should be remembered that Eisen and Belman (1953) found that simple chemicals apparently vary in their affinity for amino acids, some combining with lycine, others with cysteine. In this connection, the reader is also referred to the work of R. L. Mayer[140] (1956 and 1957). In this article, experimental evidence indicates that the type of carrier protein, whether fibrous or globular, largely determines the form of allergy induced.

Probably the first report of neomycin sensitivity to appear in recent months was the one by Epstein[68] in the foreign literature. It is of interest, however, that in 1952 Ludwig and Baer reported allergic sensitivity to neomycin. It is important to remember that patch tests in sensitized patients may give negative results. Sensitivity can be proved by intradermal tests with 0.05 cc of 1:1000 and 1:100 solutions of neomycin. These produce papular reactions in forty-eight hours. At the meeting of the Society for Investigative Dermatology in June 1957, it was emphasized that allergic contact dermatitis produced by neomycin is usually slow to develop, slow to spread and is often dry and scaly rather than vesicular and wet. Occasionally typical vesicular eczematous eruptions are caused by neomycin. Perhaps the absence of a patch test sensitivity with neomycin is further evidence that eczematous and tuberculin-type sensitivity have some immunologic features in common, but are not identical.

Sheard and others[230] described four additional cases of granulomatous reactions to deodorant sticks which contain, among other items, zirconium.

Zirconium is utilized as a deodorant in the form of a complex salt. The common name for this salt is sodium zirconium lactate. Once developed, the granulomatous reaction of the axilla does not respond to local treatment but may subside over a period of months. The present investigation has failed to reveal how zirconium may penetrate into the dermis. Abrasion from shaving was a possible factor in the three women reported. The male patient did not shave the axillary area. No further mechanism is recorded in this paper.

Various barrier creams were used by Herrmann[106] in a comparative investigation of the protective action of these creams with and without silicone oil. Nine different barrier creams were employed in the study. Patients with skin lesions, presumably caused by contact with water or aqueous solutions such as detergents and soda, showed more improvement when Kerodex 71 was used. Patients with skin lesions resulting from contact with oils, grease, dirt, paint or organic solvents were better protected by Kerodex 51.

In many industrial plants, waterless skin cleansers are used primarily for the rapid removal of tenacious soils. Modern waterless skin cleansers are classified according to their primary cleansing ingredients: (1) petroleum oil or solvent; (2) soap, ammonia, or alkali, and (3) a system of wetting agents. Some cleansers may be mixtures of (1) and (2) or (1) and (3). Goldman and others[94] studied the effects of various cleansers in patients with hand dermatitis, acne, diaper dermatitis, in cleansing routines in fungous infections—especially of the feet, infantile eczema and atopic dermatitis, cleansing routines for ulcerations and as an ointment base for various dermatologic medications. Three so-called waterless cleanser creams were used in 3,065 patients. The type preferred was the cream form of the wetting agent system. The cleansers were somewhat more effective in cases of chronic hand dermatitis, but were only of limited usefulness in other dermatologic conditions.

Tas[246] made patch tests with several barrier creams on 300 patients, most of whom were suffering from eczema. Some of these agents were water-resistant or oil-resistant creams and others belonged to the silicone barrier group. A high incidence of positive reactions of the primary irritant type were noted. It was further stated that the high incidence of positive reactions to some creams does not detract from their considerable prophylactic usefulness. The conditions during actual usage are not comparable to those of the patch test.

Johnson[116] described a comprehensive approach to the diagnosis and treatment of vesicular eruptions of the hands. Causative factors are divided into endogenous and exogenous and in addition, influencing or aggravating factors must be considered. Endogenous factors include "ids" (fungi, bacteria, chemicals); dyshidrosis (heredity, stress); eczema (foods, inhalants, bacteri, virus), and drug reactions. Exogenous factors include contact dermatitis (environmental contactants, cosmetics, topical drugs); infections (bacteria, fungi, viruses, parasites), and physical allergy resulting from cold and light. Influencing factors include friction, xerosis, endocrines, avitaminoses, hydration, climate, psyche, familial and other stigmas.

Much information may be obtained by the sites of localization. Dyshidrosis favors the palm and sides of the fingers; scabies favors the wrist and web areas, and pustular bacterid favors thenar and hypothenar areas on the volar aspect of the hands. On the dorsal surface of the hands, yeast will invade the webs and the periungual areas while dermatophytids appear on the sides of the fingers and physical allergy (sunlight) may

appear as a single oval patch in the center of the dorsal surface of the hands. The most frequent causes of vesicular eruptions on the hands are environmental contactants. Frequently the offending agent is not so readily apparent and its discovery may require skillful observation, interrogation, and the deductive genius of a Sherlock Holmes. Exogenous factors include occupational exposures, housekeeping, clothing and jewelry, hobbies, cosmetics, food preparations (especially citrus, celery, onions, parsnips, as well as spices and condiments), topically applied medicaments, weed oils and plants.

Diagnostic laboratory procedures, patch tests and the use of the elimination diet in the management of vesicular eruptions of the hands are outlined. For moist and oozing skin lesions, aluminum acetate solution, 1:40, epsom salts, or oatmeal applied for one hour four to six times daily will provide relief and remove accumulated exudations and previously applied medicaments. For infected lesions, silver nitrate, 1:1000, or benzalkonium chloride, 1:5000, is the solution of choice. If the skin lesions have acquired an odor, the best preparation is potassium permanganate solution, 1:3000. When secondary infection is present, suitable antimicrobial drugs should be used. Antihistaminics may be given orally. After weeping and edema have subsided, zinc oxide ointment, zinc oxide paste or calamine liniment may be used. In some cases, superficial x-ray will result in improvement.

Hollander[109] stated that although soap, detergents and the macerating effect of water are causes of hand dermatitis, they are not usually the entire underlying factor in the development and duration of this disorder. Alkalies must be avoided. Other irritants and primary sensitizing agents, as well as trauma, should be minimized. Overtreatment causes further difficulty. To counteract any defatting damage that has occurred, a patient may apply small amounts of lanolin, U.S.P. cold cream, Crisco, or white petrolatum. Administration of vitamin B complex helps to achieve more complete keratinization of the skin. Ascorbic acid is also recommended.

Differences of opinion often exist between investigators as to the effect of detergents on skin conditions. Brunner[30] commented on the work by Suskind[243] of the Kettering Laboratory in Cincinnati by stating that it is a well-known clinical fact that women engaged in housework suffer from hand dermatitis much more frequently than do those in other occupations in which frequent contact with surface-active cleansing agents does not occur. It has been impossible in these clinical cases to effect a cure without strictly prohibiting contact with soap and synthetic detergents. Brunner (1954) has shown that the concentration and temperature of the detergent bath and the frequency of exposure and its duration are important factors in determining the number of reactions in these studies. Women are more susceptible than men, and the winter months render subjects much more reactive to the irritating effects of detergent soaking. The usage concentrations of detergents are sometimes substantially higher than the 0.5 per cent used in the detergent bath by Suskind. Suskind believed from his studies that dermatitis of the hands, including the eczematous dermatoses, is not made worse by isolated, repeated immersion of the hands in solutions of at least two household washing products under conditions of concentration, temperature and duration comparable to that of usage. Other factors which account for housewives' eczema are the components of dish and laundry soilage, food dyes, meat, fruit, vegetable juices, metals,

solvents, fabrics, physical factors, bacterial and fungal infection, and even the tension and stress of the social environment.

Many studies have been carried out in an attempt to determine the causal relationship of primary irritants and sensitizers in dermatitis of the hands. Thyresson and others[250] studied the effect of triethanolamine in cosmetic hand lotions used by housewives. All patients showed positive epicutaneous reactions to one hand lotion and its triethanolamine content. There seemed to be a relationship between the use of this particular hand lotion and the subsequent use of new synthetic detergents in home laundries and dishwashing.

Bandmann and Reichenberger[13] reported that allergy to eucerin is rare. Such an allergy was found in ten of 4000 patients with dermatitis who were tested. In one patient, a bullous dermatitis probably resulted from eucerin and in another, a dermatitis of the hands was probably caused by eucerin. Detailed testing with the constituents of eucerin was carried out. Mineral oil (the solvent for eucerin), petrolatum and cholesterol (contained in amounts of 30 to 35 per cent in eucerin), revealed lanolin alcohols to be the cause of positive epicutaneous reactions in nine patients. The same group of substances is the cause of hypersensitivity to lanolin. Eucerin is the same or essentially the same preparation as Aquaphor and Nivea in the United States. In a highly selected group of patients at the Skin and Cancer Unit, Postgraduate Hospital, New York, a 4.4 per cent group of patients were found to be sensitive on patch testing with lanolin. Among the ointment bases presently used, it is the impression that carbowax bases and lanolin have the highest sensitizing potential.

In discussion[132] of a case of questionable occupational contact dermatitis, an important point was developed by Wolf.[264] The patient, at the time of presentation, had an almost universal eruption with a clinical resemblance to atopic dermatitis. There was a known background of contact, but a positive stand could not be taken at this time since the initial phase of the dermatitis was in the background. The general practitioner treats the patient first and then he is later seen by specialists. True contact dermatitis may develop into true atopic dermatitis in those patients with the proper constitutional background. How is one to judge months or years after onset of the initial alleged contact dermatitis? Cipollaro[40] in further discussion stated that this is a well-defined pattern. In an individual with an allergic background, an acute contact dermatitis may follow exposure to many contactants. The acute process subsides and is replaced by a neurodermatitic type of reaction which is chronic and persistent, and often such an individual experiences an acute flare-up. A further possibility in this type of case was suggested by Ingram[114] in discussion. Since an erythroderma is now present, the question of lymphoma or mycosis fungoides may arise. The reviewer finds this one of the most difficult problems in consulting dermatology. It is often possible, however, to come to a provisional and final diagnosis by contacting the first physician who treated the patient. A careful initial history and description of the disorder are exceedingly helpful in determining whether the patient initially had a contact problem or he was primarily an atopic individual in whom additional contact factors are now involved.

Chromate dermatitis is a common cause of disability in industry. In approximately 10 per cent of all compensation claims filed for industrial dermatitis, chromium salts are the causative factor. Common sources are found in manufacturing processes, including match making, photography, mordanting, textile printing, dye manufacturing, fur dyeing, electroplating,

photoengraving, lithographing and chrome plating, as well as the manufacture of ink and paint pigments. Chrome salts are also seen in the blueprinting, painting, anodizing, canning, cement, and fur dyeing industries, and in the direct preparation of chromic acid and chromic salts. In addition to these sources of exposure, Bernhardt[18] presents a new source in the form of "prime" paints used in the aviation industry, which have a chromium salt base. It is important to remember that chromate dermatitis is notoriously slow to heal and often assumes a nummular configuration.

Zina[269] believes that a skin reaction to potassium dichromate can be considered proof of a specific allergic sensitivity. Patch tests with 0.5 per cent potassium dichromate were made on 139 construction workers with dermatoses. The reaction was negative or insufficient in thirty-three, and strongly positive in 101. Analytic studies disclosed the presence of chromate salts in the Italian cements. Even in cases of leather dermatitis, chromate can at times assume the role of specific allergen. The question arises whether the coexistence of sensitivity to chrome and cobalt and chrome and nickel is the result of an immunologic relationship between the two metals or is an expression of the susceptibility of the patient to multiple specific allergic eczematous sensitization. The latter possibility is favored by Epstein (1955).

An eruption on the feet and one which appeared on the hands following the wearing of leather gloves was traced to chromium salt used in the tanning of leather.[147] This agent is basic chromium sulfate. Patch tests with 0.2 per cent solution of this antigen elicited strongly positive results. Following a remission, an eruption of both the hands and feet again developed after the patient had worn leather shoes for two days.

Marcussen,[139] in discussing the spread of nickel dermatitis, stated that men tend to acquire nickel dermatitis through occupational exposure, whereas women become sensitized to the nickel in jewelry and clothing (clasps, fasteners, zippers, and so forth). Spread of nickel dermatitis seems to include spread from hands to face and feet, especially in men employed as nickel platers. This apparently results from contamination with nickel particles. The second form of spread to the arms, particularly the cubital flexures, seems to be independent of the primary eruption but depends mostly on the degree of sensitivity and duration of the eruption.

In response to a query regarding irritation of the skin from metals, it was stated[196] that there is no known entity that causes metals to tarnish and irritate the skin. Irritation from metals (redness, swelling and itching) may result from trauma or from sensitivity, especially to nickel in various alloys. The tarnishing of the metal arises from the moisture and the sulfur in the perspiration, which is in the form of sulfhydryl groups.

Thomas[249] has reviewed some of the allergic problems related to dentistry. One patient sensitive to Karaya gum, which is present in many foods as well as bulk laxatives and in wave-set materials, showed a positive patch test to this substance on the labial mucosa. The rectal and vaginal mucosa reacted in a similar fashion. Fisher's report on acrylic denture materials has been previously abstracted in dermatologic reviews. Allergy to baxin in dentifrices as well as procaine and pontocaine are discussed. Stomatitis medicamentosa, contact stomatitis and the relationship of dental foci to chronic urticaria are discussed.

Douglas[63] noted an increasing incidence of stomatitis which he traced to the use of dental powders or creams containing fluorides. One hundred and thirty-three patients were observed and it was noted that stomatitis cleared when fluoride preparations were discontinued. The lesions were

usually shallow, superficially ulcerated areas with a whitish exudate on the surface and adjacent areas. Treatment consisted of changing the dentifrice and painting the ulcerations with a 10 to 20 per cent silver nitrate solution. Simple mouth washes and cessation of smoking were also advised.

Reiss and others[207] performed patch tests with solutions of certain black hair dyes on 1,024 hospitalized male and female patients who were suffering from generalized systemic chronic disorders, but who also were free from any skin difficulties. These patients did not have any history of allergic disease. Three test solutions were used. The first contained paraphenylenediamine, the second contained paratoluylenediamine and the third solution contained soaps, detergents, ammonia and resorcinol. Eight persons in this group were found to be sensitive by patch test. Three patients reacted to paraphenylenediamine. Four reacted to the black hair dye containing paratoluylenediamine and one reacted to both dyes. The older age groups seemed to be more susceptible. The skin tests were repeated at intervals of three to four weeks. No change in patch tests occurred in 301 persons on retesting and on sixty-seven persons who were patch tested more than once.

Conley[48] pointed out that the toxicity problems of cosmetics are the same as those of other household contactants such as antiseptics, disinfectants and cleaning agents. Cosmetics, however, have an added problem in that cradle-to-grave skin contact is involved. Ingredients in cosmetics are increasing in number and their formulation is steadily expanding. A diversity of sensitization phenomena exists. Cosmetic reactions are an inevitable consequence of the rapidly changing technology in this field.

Plastic material that can be fashioned into artificial fingernails has become available. The acrylic liquid and powder used in artificial nails do not require heat polymerization but will polymerize and harden at room temperature. Polymerization of a mixture of methyl methacrylate monomer and polymethyl methacrylate powder with an organic peroxide and an accelerator or promoter can be accomplished. This preparation may sensitize some individuals, and patch tests were performed by Fisher and others[77] on four patients who were shown to be allergic to the methyl methacrylate. Dystrophic nail changes as well as paronychia may persist for several months. There are some differences between the clinical appearance of nails affected in this manner and the appearance of nails that are damaged by the plastic nail polish undercoat which consists of phenol formaldehyde and synthetic rubber.

Rubin[217] reported the case of a thirty-six-year-old white woman in whom an eruption had recently appeared on the index finger and thumb of the right hand. This was traced to rosary beads made of some wooden material, and was probably caused by the lacquer. The patient had never had any difficulty with glass beads.

Colldahl and Fagerberg[45] studied the effect of hypersensitivity to epinephrine in the production of conjunctivitis and eyelid eczema. It has been stated that both synthetic epinephrine and that produced from animal tissue may cause urticaria, local necrosis with pigmentary scars at the site of injection, and a combination of bronchial asthma and urticaria, or vasomotor rhinitis. A case is reported of a forty-nine-year-old woman with bronchial asthma; severe itching developed in and around the eye, accompanied by intense conjunctivitis and edema of the lids. This was traced to a hectalin spray containing epinephrine; a 10 per cent solution produced a strongly positive reaction.

Dermatitis caused by creaseless fabrics was studied in Oslo.[6] The fabrics

were rendered creaseless by treatment with formaldehyde or formalin, and traces of this agent are liable to linger in the material. Positive patch tests with moistened fabrics were obtained in sensitive individuals, and special marking of such textiles to warn persons susceptible to formalin dermatitis was recommended.

In response to a query regarding contact dermatitis of both heels, it was stated[192] that the diagnosis of contact dermatitis caused by shoes is difficult, as many dermatoses have clinical features closely resembling contact dermatitis resulting from footgear. Conditions to be differentiated are atopic dermatitis, eczematoid dermatitis, dermatitis herpetiformis, so-called pustular psoriasis, and sometimes infections due to Trichophyton and other fungi. A good summary of the investigation of such a problem was recorded by Shatin and Reisch in 1954.

Gaul[90] believes that routine patch testing with rubber chemicals is a safe and quick method for detecting sensitivity. Most of the positive reactions were found in patients with a dermatitis affecting the hands or feet, or both. At first, 1 per cent concentrations in petrolatum of monobenzyl ether of hydroquinone, mercaptobenzothiazole and tetramethylthiuram monosulfide were used. Six men and five women were found sensitive to monobenzyl ether of hydroquinone. This antioxidant produced rather violent clinical manifestations with a resemblance to severe Rhus dermatitis. Two cases resulting from contact with toy balloons were noted. Eleven patients reacted to mercaptobenzothiazole. Twenty patients were found sensitive to tetramethylthiuram monosulfide, which is an accelerator. Six of these patients had had a shoe dermatitis at some time. Four patients discovered that using germicidal Lifebuoy soap induced a recurrence of the dermatitis. Patch test concentrations are recorded for a number of antioxidants and accelerators found in rubber. Monobenzyl ether of hydroquinone is used in white sidewall tires, hospital sheeting and footwear. Another antioxidant, phenyl-beta-naphthylamine is used in tire treads, carcasses, tubes, wire insulation, footwear and high carbon stocks. Accelerators can be found in tire stocks, inner tubes, wire insulation, footwear, clothing, mechanicals, drug sundries and calendered stocks.

Sidi and Hincky[232] reported their observations on allergic sensitization to adhesive tape. Reactions to this material have been reported by many observers. Until very recently, all tapes contained zinc oxide, natural rubber, and substances derived from coniferous resins. Of all the substances in adhesive tape, resins and turpentine cause the highest number of reactions, closely followed by rubber as a causative factor. The possibility of cross-sensitization with agents closely related to substances found in adhesive tape is mentioned. Patients allergic to acyclic terpenes may possibly have a cross-sensitivity to lavender, geranium vervein, saffron, carrot, tomato, and citrus peels. Sensitization to natural rubber (polyisoprene) may bring about cross-sensitization to the acyclic terpene group. It is stressed that more observations in this field of cross-sensitization are needed. Sidi was able to prepare a hypoallergenic adhesive tape. This apparently is available in Europe under the trade name "Neodermotests." Elasticized bandages made with hypoallergenic adhesive tape were useful in stasis syndrome, ulcers, occlusive dressings in selected dermatoses and for some cosmetic purposes.

In last year's *Dermatologic Review* I failed to stress that eczematous eruption was not present under the adhesive tape in patients showing periorbital dermatitis as described by Reyer.[209] Apparently the adhesive strapping was not locally sensitizing. The antigen appears to consist of a body

tissue plus bacterial toxins. If the skin of the eyelids is already sensitized, a dermatitis may develop when greatly increased amounts of metabolites have suddenly entered the circulation.

Hollander[108] described the case of a forty-eight-year-old housewife who had a vesicular dermatitis of the ring and small fingers of the right hand and patchy areas on the neck of one year's duration. All efforts to determine the etiology were futile until the patient volunteered the fact that she cleansed her jewelry in ammonia water. A patch test with a necklace which had been washed in ammonia water elicited positive results. No further treatment was needed to clear her skin, except abstaining from this method of jewelry cleaning.

It is suggested[181] that when a dermatitis resulting from chlorinated water develops, crystals of sodium thiosulfate (Antichlor) in the sink and a handful in the bathtub would be helpful.

In response to a query regarding cases of dermatitis of the hands produced by Celeron, it was stated[193] that this preparation is a phenolic-formaldehyde resin and that the eruption results chiefly from the formaldehyde component. Formaldehyde is a potent sensitizer and it has been known to sensitize members of a worker's family just from contact with the clothing of such a subject who was working with phenolic-formaldehyde resins. With or without treatment, the dermatitis is likely to persist or to recur upon re-exposure of the subject.

In answer to a query regarding allergic dermatitis in a meat packer who uses cellophane paper in her work, the consultant[183] stated that contact dermatitis is not common in meat wrappers. Eruptions resulting from cellophane are also unusual. It must be admitted that sensitization to the fumes that emanate from the heated cellophane and are produced by closure of the packages could develop. Thorough study of this patient with careful patch tests was advised. The cleaning agents utilized around meat blocks and counters are a more likely source of dermatitis than cellophane.

The causative role of molds in atopic dermatitis is well known. Contact dermatitis resulting from molds seemed a possibility to Epstein and others.[70] Atopic dermatitis caused by protein fractions of the molds is an established entity and the possibility exists that contact dermatitis resulting from the ether-soluble oleoresinous fractions could conceivably produce positive reactions and clinical hypersensitivity. Patch tests with oleoresins of molds produced only one positive reaction to helminthosporium among 135 patients, many of whom were persons with contact dermatitis of unknown origin. Contact with molds was considered a possibility. The one patient with a positive reaction suffered from atopic dermatitis aggravated by house dust sensitivity and benefited greatly from desensitization with dust.

Voldánova[252] studied 1,000 patients with contact dermatitis who were hospitalized in Prague between 1953 and 1955. The highest incidence (17.9 per cent) was observed in salaried patients in whom dermatitis was usually caused by topical medicaments. This was followed by workers in automobile, paint and heavy industry (17.7 per cent) and domestic helpers (14.6 per cent). The lowest incidence was found in miners (1.1 per cent), hairdressers (0.9 per cent) and shoe makers (0.5 per cent). The cause of contact dermatitis was suspected in 70.6 per cent and confirmed by patch tests in 27.4 per cent.

Five hundred workers employed in the manufacture of antibiotics were patch-tested for evidence of acquired sensitivity to penicillin, streptomycin, tetracycline, and tyrothricin-xanthocillin combination. Comparison of the

results with control tests on persons engaged in other areas of employment showed a decided increase in the rate of sensitization among the workers from the antibiotics plant.[124] Although sensitization as such is not compensable, the affected employees are entitled to be informed of their increased sensitivity to the drugs which, in the case of illness, may be of vital importance to them.

Baer and Witten,[10] with their leading article in the *Year Book of Dermatology and Syphilology,* continued to describe allergic eczematous contact dermatitis. While much is known with respect to clinical diagnosis, finding of causal factors and management of the disease in its various phases, the major remaining unsolved facets are the prevention of this form of sensitization and practical methods for abolishing established sensitivity. Various tables are appended, especially in the 1958 Year Book, with useful information regarding common agents used for patch testing.

Dermatologists who deal with industrial contact dermatitis are familiar with the process of "hardening" or the development of immunity of the skin. Some investigators do not believe that such a phenomenon occurs. Morris[149] described four such cases which he has observed. In two cases the condition was caused by sensitizing agents (zinc and black printer's ink), and in two by irritants or potential irritants (tar oil and naphtha). An opinion was expressed that workers need not be changed from a particular job on development of nonincapacitating dermatitis to allow for the process of "hardening" to develop.

According to Donaldson[61] (Rehabilitation, 1957, p. 36), the great dermatitis myth of the twentieth century in England is the belief by many patients that nearly all skin diseases are occupational. The myth is further favored by the present system of compensation under the Industrial Injuries Act. Dermatologists recognize that many factors may operate in the production and perpetuation of skin lesions. The busy general practitioner and the factory medical officer can be responsible for iatrogenic invalidism by giving hasty opinions on skin lesions.

The Committee on New and Unused Therapeutics of the American College of Allergists[208] undertook to study a new antihistamine called Theruhistin. This preparation is anticholinergic and antiseritonic and has a wide application as an adjuvant in the treatment of allergic disease. In the therapeutic range, this preparation has been found to be devoid of any acute or chronic toxicity and is well tolerated by all age groups. The average dose is 4 mg three to four times daily. Of seven patients with urticaria and eczema, four obtained excellent results, one a slight effect and two were not changed.

Spielman[237] used one 12 mg sustained action Theruhistin for seven patients with contact dermatitis and found that all seven were subjectively relieved. The most outstanding feature of this new antihistaminic agent is its lack of side effects as well as its great potency. In the entire series of 200 patients with various allergic disorders, only one complained of drowsiness.

ATOPIC DERMATITIS

Reed and others[204] studied vascular reactions in chronically inflamed skin, particularly white dermographism which is present in cases of atopic dermatitis. White dermographism is the vasoconstriction of minute cutaneous vessels and is seen after light stroking of normal skin. In chronic inflammation of the skin it persists after both light and heavy stroking. White dermographism depends on mechanical stimulation of the

skin and apparently is independent of any chemical or neural stimulus. The condition can be seen not only in cases of atopic dermatitis but in psoriatic erythroderma, mycosis fungoides of the infiltrative type and lymphomatous erythroderma. When the diseased skin returns to normal, white dermographism disappears and is replaced by normal "triple response" to mechanical stroking. A number of drug agents, including atropine, benadryl, procaine and saline, were injected into these patients, but these agents had no effect or inhibition on the appearance of the white reaction produced by stroking. The second section of studies on vascular reactions in inflamed skin by Reed and Kierland[203] involved the use of a number of agents including epinephrine, Regitine, acetylcholine and their relationship to the "delayed blanch." The intradermal injection of epinephrine produced a normal reaction in chronic inflammatory conditions but a somewhat reduced reaction in acute inflammatory conditions. The intradermal injection of Regitine inhibited the reaction of epinephrine in the skin. The delayed blanch noted after intradermal injection of acetylcholine is characteristic of atopic dermatitis. It is present only in the involved areas of skin. The delayed blanch was inhibited in part or completely by the intradermal injection of atropine but not by injection of Regitine, Benadryl or procaine. This reaction to acetylcholine and other cholinergic drugs, when present, may be used to differentiate atopic dermatitis from similar inflammatory cutaneous diseases. In a continuation of the studies of vascular reactions in chronically inflamed skin, Reed and others[205] reviewed the action of histamine and the histamine releaser 48-80. The flare response to intradermal injection of histamine and 48-80 in patients with dermatoses was studied. Patients with atopic dermatitis showed strong reactions to histamine as well as to 48-80. Reactions were minimal in patients with disseminated neurodermatitis, psoriatic erythroderma and mycosis fungoides. The flare response to histamine depends upon the acuteness of the inflammation present. The flare can be reduced or abolished in patients who have white dermographism when the affected area of skin is rubbed before or after the injection. Histamine-induced pruritus may be reduced by stroking the skin and thus abolishing the flare response by producing vasoconstriction of the minute vessels of the skin. Nicamin, an ester of nicotinic acid, does not produce a delayed blanch when injected intradermally. Any study of percutaneous absorption in patients who have white dermographism will be influenced by the strong tendency toward vasoconstriction when the skin is traumatized.

Kalz and others[118] studied vascular skin responses in atopic dermatitis with special reference to the influence of psychological factors. Previous studies had already elicited the "white dermographism" in atopic dermatitis. Others had reported swifter cooling of the skin in a cool environment and delayed warming in a warm environment in atopics as compared with normal persons. This observation suggests a tendency to peripheral vasoconstriction in atopics. The cold pressor test in atopics is likely to show a greater rise of blood pressure than in normals, and it was also observed that the normal flare of a histamine wheal was absent in atopics. It was demonstrated that persons with atopic disease other than dermatitis showed changes similar to those in patients with atopic dermatitis. Absence of flare and minimal pilomotor and sweat response to acetylcholine have been shown in atopics. Intradermal injection of acetylcholine in atopics is followed by blanching over the site of injection. Emotional instability and phobic and obsessive-compulsive symptoms were found by some authors to be prominent in atopics. In another study, some atopics showed emotional lability

with a tendency to hysteria and others showed rigidity with a tendency to compulsiveness. The hysteric class tended to retain the disorder for longer periods of time. In this study, Kalz and others found that patients with a normal response to intradermal histamine showed a tendency to display their emotions and especially their aggressive drives freely. When histamine flare was absent, the patients showed a tendency to restrain the display of their emotions and aggressive drives. In this category, a flare developed if the patients were retested after an interview directed to relieve and discharge previously inhibited aggression. Recent unpublished observations by Davis and collaborators (Walter Reed Army Hospital, Washington, D. C.) and Allene Scott (St. Bartholomew's Hospital, London, England) indicate that the absence of histamine flares in atopics is not the result of vasoconstriction but of increased vascular permeability and subsequent edema, caused by acetylcholine release. In a discussion of this paper, Rothman[216] stated that the vasoconstrictor tendency in atopic patients is the result of increased sensitivity and exaggerated responsiveness of the contractile elements of the small blood vessels and that this reaction has no connection with the nervous system. There is little doubt that cutaneous vascular reactions of patients with atopic dermatitis are abnormal. Previous reports have stressed the delayed blanch phenomenon which has been interpreted as a paradoxical vasoconstrictor response to acetylcholine. This phenomenon consists of paleness developing at the acetylcholine-induced wheal and slowly spreading peripherally after three to five minutes. Davis and Lawler[54] reported observations on the delayed blanch phenomenon in atopic subjects, utilizing direct microscopic visualization of the superficial vessels. These observations led to the belief that the delayed blanch is caused by edema and not vasoconstriction. It was observed that the capillaries in the areas of the acetylcholine-induced wheal and delayed blanch reaction remained dilated even though the areas turned pale grossly. In discussion, Lobitz[135] produced further evidence based on desiccation of skin tissue, but this whole subject seems to be controversial.

In response to a query regarding generalized atopic dermatitis in an eighteen-year-old girl who had suffered since infancy, one consultant[180] stated that this problem taxes the skill of even the experienced dermatologist or allergist. In such a case, steroids and corticotropin should be used only for an emergency or while the patient is hospitalized for investigative purposes. Allergic, dermatologic and psychiatric investigations were suggested. A second consultant likewise agreed that this was a difficult problem and suggested that this patient be advised to limit the amount of work or perhaps discontinue school for a year. Hospitalization with rest in bed and use of simple soothing lotions, ointments and baths often will benefit the sorely distressed patient. Steroids are of value, especially in this regard, but they should be employed only under most careful supervision and their use should not be continued for any length of time for fear of the effects of withdrawal. Diet seems to play a minor role when atopic dermatitis has persisted into adult life. This is true regardless of skin tests. A change in climate was recommended. Discussion with the patient and parents, explaining the large emotional element entering into the picture, often will be of benefit.

Milder[145] studied patients from the eastern agricultural districts of Czechoslovakia. Eighty-four patients were found to have atopic dermatitis among approximately 8,000 cases of eczemas and dermatitides. Tests with ingestant and inhalant allergens were of no value in adults and of very questionable value in the children. The allergic factors may be considered

to cause exacerbations in some cases, but the allergic sensitivity is of little etiologic importance. Eighty per cent of patients came from agricultural areas and 20 per cent from industrial areas. Of patients affected, however, 64 per cent came from industrial environments, and the less stressful environment of the farmer was thought to be responsible for the lower figures reported in agricultural regions (36 per cent).

Autoeczematization is the process by which a widespread dermatitis may complicate several types of localized eczema. The clinical course of patients in whom generalized autogenous eczema developed is described and histologic studies are presented.[267] At certain clinical stages, cases of neurodermatitis (local and generalized), nummular eczema, exudative discoid and lichenoid chronic dermatosis, and dermatitis herpetiformis bear a striking resemblance to individual stages of generalized autogenous eczema. These dermatoses commonly have an allergic background and are often associated with emotional problems. These observations suggest that these conditions belong to the same group of diseases. Strauss and Kligman[239] studied the relationship of certain atopens to the production of atopic dermatitis. Eight men with strongly positive reactions to one or more atopens were selected for study. None had atopic dermatitis but five had bronchial asthma, one had hay fever, and one a history of acute urticaria. All were sensitive to Rhus antigen, and allergic contact dermatitis could be provoked by patch testing with pentadecyl catechol (PDC). In three subjects, dermatitis produced by PDC was intensified by the addition of specific antigen (ragweed 1:20) applied locally. Higher dilutions of PDC produced reactions in patients given increasing doses of atopens subcutaneously. Protein antigens are considered to be secondary agents which cause exacerbations in previously damaged skin.

Edmundson and Guy[191] believe that the etiologic factors in atopic dermatitis and in duodenal ulcer, ulcerative colitis, migraine, and some cases of asthma and rheumatoid arthritis appear to be similar, if not identical. Atopic dermatitis is believed to be a stress complex with the skin acting as the organ which reflects the emotional tone of the individual. Psychiatric management, especially in groups of such individuals, appears to be useful as adjuvant therapy. The use of steroids, locally or parenterally, or both, is of considerable value in the control of exacerbations of atopic dermatitis. Tranquilizers and sedatives rarely have demonstrable effectiveness. Criep[50] reviewed the records of 157 patients with atopic dermatitis. When standard allergic management was used, decided relief was obtained in 62 per cent, moderate relief in 27 per cent and no relief in 11 per cent. Younger patients had a better percentage of improvement. Emotional factors were predominantly present in most of the patients of this group and frequently affected the outcome of treatment.

The most common skin disease in children treated by allergists is eczema. Eczema or acute dermatitis, according to Waisman,[253] requires applications of a moist agent. This agent should be cold if the eczema is the result of contact irritants. If bacterial infection is present, warm to hot moist agents should be used. These include physiologic saline solution, boric acid solution, magnesium sulfate or aluminum acetate. When extensive areas of the body are involved, baths are helpful. At night an oily preparation like calamine liniment is well tolerated. Mycostatin suspension is effective in acute monilial dermatitis. Crump[52] reviewed the management of the allergic child. As far as infantile eczema is concerned, it is called the most difficult, trying, and frustrating problem of all infant allergy. The author described two successful methods of therapy to be used when all

other methods have been tried. They are autohemotherapy, and the very careful use of liquor potassii arsenitis (Fowler's solution). The reviewer notes that most modern dermatologists have discarded the use of Fowler's solution in routine therapy.

Barker and others[14] presented a differential clinical study of erythrodermas of infancy, with particular reference to exfoliative dermatitis of Ritter's and Leiner's disease. Ritter's disease is probably a pyoderma appearing very early after birth (from one to ten days). This condition generally responds to antibacterial management. Leiner's disease is probably related to seborrheic dermatitis and may represent a biotin deficiency. Steroid therapy may be helpful. In one patient of this study with Leiner's disease, typical psoriasis developed after he had been symptom-free for fourteen months. Psoriasis was still present when he was last seen at the age of six.

Brunsting had previously reported the occurrence of cataracts in a group of 1,158 patients who had atopic dermatitis. In 136 patients, structural changes in the lens were consistent with the type of change shown to be associated with atopic dermatitis.[31] Of these 136 patients, seventy-nine had grossly obvious cataracts that impaired the vision, while fifty-seven had cataractous changes detected only by means of the slit-lamp microscope. Of the fifty-seven patients, thirty-six replied to a questionnaire and twenty subsequently underwent eye examination. Six had difficulties with their eyes. With regard to the condition of the skin, nine patients had "clear" skin, fifteen had slight difficulty with the skin and twelve had moderate to pronounced difficulty. This last group of twelve patients included the six who had ocular difficulties.

Brain and others[23] discussed generalized herpes simplex and reported the development of Kaposi's varicelliform eruption in an eczematous child. This occurred in a boy nine months of age who was hospitalized because of severe eczema. He was treated first with cortisone orally and later with hydrocortisone ointment locally. Two additional children with "infected eczema" were admitted to the same ward; herpes simplex was suspected and later proven in one of them. The child in whom Kaposi's varicelliform eruption developed was treated intensively with antibiotics and given two doses of gamma globulin. He appeared to improve at first, but on the eighth day of his illness, his condition deteriorated rapidly and he died eleven days after the onset of the herpetic eruption. Sudden collapse before death suggested extensive involvement of the adrenal glands, which was shown at necropsy. Gamma globulin in doses of 0.1 cc per pound should be given before or immediately after exposure to all cases of infantile eczema on admission to the hospital. This should be repeated four to six weeks later should the child remain in the hospital. A seventeen-year-old white girl is described[220] who had eczema herpeticum with severe systemic effects. Symptomatic treatment, including penicillin, was not effective. On the fifth day of the illness, an intramuscular injection of 4 cc of gamma globulin was administered. On the following day, another 20 cc of gamma globulin was given intramuscularly. Antibiotics had been discontinued. No new lesions appeared after the second day of hospitalization. It was felt that the disorder was promptly controlled by gamma globulin. The reviewer notes that while this article makes a clinical distinction between eczema herpeticum and eczema vaccinatum, most writers believe that this distinction is not possible clinically.

Milk substitutes have in the past played a large role in the management of infantile eczema. Fries[88] found that while 5 per cent of his patients

reported clinical symptoms referable to cows' milk, allergy to milk could be proved in less than 0.3 per cent. It is noted that a food can cause gastrointestinal symptoms from nonantigenic components. For example, the toxic hemagglutinating component of soybean may be present in trace amounts after processing. The physical properties of some milks, poor preparation or bacterial contamination may account for symptoms which are sometimes attributed to hypersensitivity to milk. Fries recommended the boiling of cows' milk or the substitute of a meat-base formula or goats' milk in preference to the use of a vegetable-base milk. Kane[119] gave a soybean milk substitute (Sobee, liquid) to a group of 102 infants ranging in age from one week to nine months. These infants had a sensitivity to cow's milk and most of them suffered from infantile eczema. This preparation proved to be nutritionally adequate and comparable in every respect to cows' milk. Weaning to whole cows' milk was usually started at the sixth month, and was successfully accomplished in 90 per cent of the cases. A number of children with various allergic complaints were given powdered Sobee, a new milk substitute.[46] Seven of the infants had eczema. The formula was well tolerated by twenty-three of the twenty-five infants. Duration of feeding was one week to five months. Weight gain was satisfactory; feces were normal in color and soft in consistency.

Pediatricians have long noted the effect of egg yolk when first introduced into the diet of infants. Symptoms most commonly encountered include refusal of the yolk and regurgitation. Skin eruptions of the eczematous type and occasionally respiratory symptoms have been reported. It is generally agreed that skin eruptions and respiratory symptoms are caused by the antigenic properties of the egg yolk or the egg white which adheres to it in normal kitchen preparation. Todd and others[251] made further studies on the antigenicity of egg yolk. Raw egg yolk is capable of antigenic stimulation, and this can best be demonstrated by both the passive transfer and Schultz-Dale tests. The sensitivity produced by raw egg yolk is separate and distinct from the sensitivity produced by egg white, although there is evidence of a separate antigen common to both. Sensitivity to egg yolk could be demonstrated to occur only with raw egg yolk and not with hard-boiled yolk or the commercial preparation, by either the passive transfer or Schultz-Dale technique. Hard-boiled yolk and commercially prepared yolk showed antigenically significant amounts of egg white antigen, although the amount was much smaller than that found in raw yolk. In spite of these findings, it is strongly advised that caution be exercised in the feeding of any preparation of egg yolk or egg white to an infant or child known or suspected of being sensitive to eggs.

Rapaport[201] described psychosomatic aspects of allergy in childhood, but believes that allergic disorders have a basic immunologic etiology. While he writes largely of asthma, the personality changes are likewise seen in children with atopic dermatitis (reviewer's note). The personality structure of allergic children has been charted to demonstrate: (1) a neurotic type of personality, (2) high intelligence on verbal tests with a poorer performance ability, (3) marked overanxiety and lack of self-confidence, (4) considerable latent aggressiveness and egocentricity, (5) a compulsive type of personality with exaggerated orderliness and cleanliness. Various modifications of this personality structure—including immaturity of behavior, seclusiveness, and moodiness with depression—have been described by other authors. In addition to carrying out allergic management, Rapaport separates the child from his family for six months to a year in

selected cases. This often has a beneficial effect on the course of the allergic disease.

In spite of all that has been said and written about atopic eczema in the last thirty years, the psychosomatic approach to this disease state has not been as widely accepted as its proponents have hoped for. Guy and Schoemaker[100] studied sixty-one patients with atopic eczema who were evaluated psychiatrically and were given individual psychotherapy, while skin care and group psychotherapy were carried out in the dermatology department. The results of these studies indicate that severe exacerbations of atopic dermatitis are associated with depression, social withdrawal, and a state of relative immobilization. Remissions are associated with increased aggressiveness. Supportive pychotherapy has provided a valuable adjunct to the standard medical treatment of atopic eczema. Robinson and others[212] presented charts as part of an intensive study of the effects of various tranquilizing drugs and controls in a series of more than 3000 patients with various dermatoses caused or aggravated by emotional tension. The ataractic drugs, thorazine, meprobamate, atarax, trimeprazine and chlorophenothiazinyl ethyl were all accorded excellent rating on the basis of their observations. No serious systemic reactions resulting from prolonged administration of these drugs with the dosage used are noted in this study. Minor adverse reactions which were encountered included dryness of the oropharynx, headache and drowsiness. Rush and others[221] studied a group of patients with chronic disseminated neurodermatitis. The study team was composed of a psychologist and a dermatologist, who met with the patients as a group twice weekly for a period of two years. It was shown that exacerbations of neurodermatitis are precipitated by emotional tension as defined in the report, and that the inflammation decreases when tension is relieved. The patient with neurodermatitis reacts to certain situations both emotionally and somatically in the primitive fashion of infancy.

Becker and others[15] studied the effect of meprobamate in 260 patients with various dermatoses. The drug was given in divided doses varying from 200 to 2400 mg per day. This was used as an adjunct to previously prescribed local therapy. While forty-three of fifty-eight patients with neurodermatitis obtained an excellent to good result, only seven of fifteen patients with atopic eczema and only four of ten patients with anogenital pruritus showed a good effect. Thirteen of nineteen patients with contact dermatitis showed good results. Meprobamate is a satisfactory sedative in the treatment of selected patients with dermatoses when the relief of emotional tension is an important factor. The lack of effective relief of pruritus, the unpredictability of dosage tolerance, the frequent side effects, and the high cost of the drug are the principal deterrents to its general use. In discussion of this paper, Beinhauer[16] as well as Woodburne[265] urged caution with the use of the tranquilizers. Woodburne noted that at the poison center at the University of Colorado, the two physicians in charge feel that at present the tranquilizers are responsible for more of their poisoned patients than perhaps any other drug. The tranquilizers potentiate the action of alcohol and barbiturates.

Benactyzine hydrochloride (Suavitil) is a member of that group of anticholinergic substances, several of which have selective activity upon various functions of the brain. This preparation raises the threshold for external stimuli, so that the patient, in a state of tension arising from excessive strain, no longer reacts to stimuli which previously would have provoked decided irritation. Welsh and Ede[257] used Suavitil alone and in combination with other therapeutic agents in the treatment of patients with derma-

tologic disorders known to be complicated or exacerbated by anxiety and tension. In the group were eight patients with atopic dermatitis and one with angioneurotic edema and urticaria. Because of side effects such as memory loss, apathy, drowsiness and nausea, it was concluded that this agent is not suitable for indiscriminate use in dermatologic practice.

Shanon[226] studied the effect of perphenazine (Trilafon) for a period of five to seven weeks in a series of 308 patients with a variety of dermatologic disorders. The majority of the patients had atopic dermatitis, neurodermatitis, urticaria, infantile eczema, eczematous hand dermatitis, seborrheic dermatitis, psoriasis or pruritus vulvae et ani. Perphenazine, in common with all ataractics, is not curative. Careful individualization of dosage is required for adequate treatment. In general, the average dose should not exceed 8 mg daily in adults and 4 mg in children and old people. Of 144 patients with itching, pruritus disappeared completely in forty-nine patients and improved in forty-one. There was no response in forty-three cases and eleven patients did not return for further examination. Good results were noticed in cases of psoriasis, atopic dermatitis and neurodermatitis, whereas in pruritus vulvae et ani, postherpetic neuralgia and hand dermatitis, no definite constant effect on itching was noted. Thomas[248] used a new antihistaminic, para-bromdylamine maleate (Dimetane), in allergic dermatosis. Eighteen patients were given 16 to 36 mg of Dimetane per day. Fourteen showed a satisfactory response. Sixteen of the eighteen patients tolerated Dimetane and two could not tolerate the drug because of side actions. The allergic dermatoses included atopic dermatitis, contact dermatitis or dermatitis medicamentosa. Lackenbacher[127] treated nine patients with atopic dermatitis of whom four had an excellent response, four had a good response, and one a moderate response to four tablets of Metreton daily in combination with Chlor-Trimeton and Vitamin C. Spielman[237] used one 12 mg sustained action Theruhistin tablet in the treatment of atopic dermatitis. Of five patients, three reported very good control of symptoms; one had fair control, and one was unchanged.

Clyman[43] evaluated three preparations in the treatment of patients with atopic dermatitis. These contained: (1) 0.5 per cent hydrocortisone free alcohol and 5 per cent coal tar extract in a vanishing cream base; (2) 5 per cent coal tar extract in vanishing cream, and (3) 0.5 per cent hydrocortisone in vanishing cream. Twenty-three patients were studied by the "symmetrical paired comparison" technique. Severe pruritus was controlled more promptly and effectively by the combination of steroid plus coal tar. The results seem to indicate a synergistic effect. Other agents which are effective with steroids in the treatment of atopic dermatitis include Vioform, Diodoquin and Sterosan. de la Fortier and Gregoire[82] reported their experience with twenty-eight cases of simple or complicated infantile eczema treated with chlorquinaldol (Sterosan). The infants ranged from one and one-half to three months of age and treatment extended over a period of two to three weeks. In 25 per cent of the patients the rash cleared completely. Improvement was noted in a further 64 per cent and slight improvement in 10 per cent. It was concluded that Sterosan is a potent bacteriostatic and fungistatic agent for topical use in the treatment of infantile eczema.

Brandt and Szolomejer[24] discussed therapeutic results after using solubilized Colorado shale oil. The preparation is now water-miscible and is available in solubilized oil form as Metashal. Results of treatment in a group of 365 pooled cases indicate that 62.5 per cent of the infants with

atopic dermatitis showed an excellent response, 31.25 per cent very good, and 6.25 per cent good or fair results. In atopic dermatitis of juveniles and adults, the results were a little less beneficial; only 27.8 per cent showed an excellent response. Fifty per cent showed a very good response, however, with 16.6 per cent good or fair, and 5.6 per cent had a slight or negative response. Baker[12] has treated 120 patients with Sandostene, a recently introduced antihistaminic which is available in tablet and ampule form. It may also be applied topically. The pruritus associated with atopic eczema, dermatitis medicamentosa, contact dermatitis and urticaria was relieved in a fair number of cases. In acute dermatoses, 10 cc of Sandostene plus calcium was given intravenously every day or every other day and this was supplemented with Sandostene tablets in doses of four to six daily. A long-acting tablet is also available. There were no side effects in this series. The reviewer notes that Sandostene has currently been taken off the market.

URTICARIA AND ANGIONEUROTIC EDEMA

A general review of the subject of chronic urticaria was presented by Wolf.[263] Exogenous causes of chronic urticaria include inhalants; injectants, such as penicillin, liver extract, insulin and ACTH; physical factors such as heat, cold and light; contact factors such as animal danders and stinging nettle and ingestants including foods and drugs. Endogenous causes include bacterial infection; parasitic conditions; endocrines and their products, and systemic diseases such as malignant neoplasms, Loeffler's syndrome, periarteritis nodosa, and Hodgkin's disease. Psychosomatic difficulties are the most frequent cause of chronic urticaria. When the cause cannot be determined, a definite plan must be followed. Foods may be checked by uncomplicated elimination diets. Sedation should then be tried and estrogens may be used in menopause. Antibacterial therapy is mentioned. Sulfasuxidine, 10 to 12 gm daily for six days, is recommended for indefinite colon dysfunction. Symptomatic treatment and management include the use of antihistamines and steroids, and in idiopathic, neurogenic or vasomotor types, vasodilatation by histamine or nicotinic acid is helpful. Thirty of eighty patients in this series obtained complete relief and thirty-two received partial relief. Eighteen patients were not relieved.

Psychogenic urticaria was known to some of the earliest writers on urticaria. It had been shown that in patients with cholinergic "urticaria," reflex heating of the skin brought about by the warming of the lower limbs produced the eruption on the unimmersed parts of the body. After further studies, it was concluded that the lesions in these patients were caused by the liberation of acetylcholine from nerve endings, which resulted in the liberation of "H-substance" and subsequent wheal formation. Garretts[89] studied two patients suffering from typical attacks of cholinergic urticaria and concluded that the small, pale papule surrounded by a large flare is not typical of urticaria of the histamine type. The structural changes in the epidermis demonstrated in two cases confirm the views of Herxheimer (1956) that the sweat apparatus is involved in cholinergic urticaria. The histologic appearances are comparable with those of miliaria. Exfoliating doses of ultraviolet rays were effective in both cases. The mechanism is not certain.

The bullous form of urticaria is so uncommon that several recent textbooks of dermatology only mention it by name. Winer[261] reported the case of a man, aged forty-six, in whom angioneurotic edema of the face, hands and feet developed. On one occasion the wheals on the right forearm be-

came cyanotic and clear blisters, measuring 3 mm in diameter, developed on their surfaces. The patient improved on an elimination diet, but when beef was added he suffered a severe relapse, with edema of the face, tightness of the throat and difficulty in breathing, and had to be hospitalized. Histologically, the blisters were subepidermal and unilocular. Their contents were of a serocellular nature, the predominant cells being lymphocytes and eosinophils. Vesicles of bullous urticaria must be differentiated clinically and histologically from dermatitis herpetiformis, erythema multiforme and mycotic dermatitis.

In response to a query regarding urticaria and purpura following the administration of penicillin, it was stated by the consultant[169] that the delayed type of reaction from penicillin, the so-called serum-sickness type, may last as long as a year or more. A period of two years is an unusually long time for a penicillin reaction to persist, but it cannot be deemed impossible. This may be the result of persistence of traces of the penicillin antigen in the tissues or preparing or conditioning of the tissues to other sensitizations or even nonspecific mechanisms releasing chemical mediators that may produce hives. The presence of small amounts of penicillin in milk make it mandatory that such a patient follow a milk-free diet for several weeks.

Bruun[32] treated six patients in whom allergic symptoms developed from the handling of coffee. Some patients had asthma and angioedema developed in others. Patients were symptom-free while on holidays when coffee was avoided. Intradermal skin tests with extracts of coffee elicited positive reactions. Boiling destroys the allergen. Sensitization to coffee may appear in a relatively short time; it may be a matter of weeks or a few months.

Innumerable cases of acute and chronic urticaria caused by parasites are cited in the literature. This condition has been seen in association with ascariasis, oxyuriasis and tapeworm infestations associated with eosinophilia. Wilhelm[260] reported two patients with urticaria in whom Giardia lamblia cysts were discovered in stool specimen examinations. Fumagillin, 20 mg four times daily, was given for ten days. After the third day, results of stool examinations were negative and the urticaria likewise subsided on the third day of treatment. Because symptoms recurred with a return of the organism in the stool, 100 mg of quinacrine hydrochloride (atabrine) three times daily was prescribed and the stools soon became normal and remained so.

Derbes and Krafchuk[58] described two patients in whom urticaria developed following inhalation of vapors from paint fumes and fish odors, as well as one patient in whom urticaria was caused by airborne ragweed pollen. This condition is called osmylogenic urticaria.

Rajka and Vincze[200] studied a new approach to the diagnosis of urticaria of the serum-sickness type resulting from penicillin. Penicillin was combined with gamma globulin using 0.005 ml of a mixture of 10,000 I.U. of penicillin and 1 ml of gamma globulin. The mixture was kept at 4° C and was used seven to ten days after preparation. In thirty-four of forty cases, positive intracutaneous test reactions were obtained with the combined testing agent as compared to sixteen when crystalline penicillin was used alone.

In response to a query in reference to operation on a child with angioneurotic edema and greatly hypertrophied and infected tonsils and adenoids, it was stated[188] by the consultant that it is possible that the angioneurotic edema was caused by the infected nasopharynx. If this is so,

there is a possibility that an operation on this focus would induce an attack of angioneurotic edema. Preventive measures with antihistamines given several days before operation were suggested. A second consultant stated that the surgical team should be prepared to carry out a tracheotomy and it was further stated that protection of this patient would be afforded if premedication included intramuscular promethazine (0.5 mg per pound of body weight the evening before operation and the same dose repeated about ninety minutes before anesthesia is induced). Narcotics were to be avoided and atropine by injection forty-five minutes before anesthesia would be helpful. To avoid excitement and struggling, thiopental, 20 mg per pound of body weight, could be instilled rectally. Ether and oxygen, with or without added nitrous oxide, is the gas mixture of choice for maintenance of anesthesia in such allergic children. The reviewer notes that this problem occurs quite frequently in allergic patients. If attention to detail is planned before surgery, considerable anxiety can be avoided for the surgical and anesthesia team.

In reply to a query on the treatment of urticaria, it was stated by the consultant[189] that an effort should be made to determine the etiology of the given case. About 40 to 50 per cent of patients with urticaria have an allergic etiology. Allergy to intestinal parasites is occasionally encountered. Psychosomatic factors are not infrequently of importance. Histamine "desensitization" does not have a logical basis in the treatment of urticaria. The second consultant stated that in a very large percentage of patients with urticaria, no allergic or other proved etiologic factors can be demonstrated. Antihistamines and, in some cases, steroids are justified in severe cases of urticaria.

Thomas[248] reported his experience with a new antihistaminic, para-bromdylamine maleate (Dimetane). A total of 140 patients were presented in this study, including those with major allergic manifestations as a diagnosis. One hundred and twenty-two patients showed a satisfactory response to the drug. Eleven patients experienced some side reactions; the most frequent one reported was drowsiness. Five in this group could not tolerate any antihistamine. Most patients were given a 4 mg tablet four times daily. Twenty-two patients were given two extentabs containing 12 mg daily and a small number of patients were given the elixir of Dimetane in the range of 12 to 24 mg daily. Six patients with urticaria and angioedema were given 16 to 36 mg per day, with a satisfactory response in all six.

Spielman[237] studied a number of allergic conditions which responded to sustained release Theruhistin. An unselected group of 200 patients was treated, and the study was carried out for a period of twelve months. Fourteen of fifteen patients using sustained action Theruhistin tablets were relieved of the symptoms of urticaria.

Lackenbacher[127] treated eight patients with acute or chronic urticaria using four tablets of Metreton daily. Of this group, three obtained excellent relief, four good effects and one a moderate effect. The steroid was used in combination with Chlor-Trimeton and vitamin C.

Eisenberg[66] reported his experience with the use of tranquilizing drugs in allergy. In the treatment of allergic individuals, these preparations can serve a useful purpose by relieving certain psychiatric states that tend to aggravate physical manifestations of the disease. It is emphasized that these drugs will not replace specific therapy for allergic diseases. Only three of twelve patients were improved with thorazine treatment. These patients had urticaria. Two of ten patients with neurodermatitis were

improved. However, six of fourteen children with eczema were improved. Three of nine patients with urticaria were improved with serpasil. Four of twelve patients with urticaria and angioedema were improved with Miltown. The tranquilizers should be used only as an adjunct in the treatment of allergic disorders, when certain states of anxiety and tension are present, and not as a replacement for accepted diagnostic and therapeutic procedures.

DRUG ALLERGY

McLetchie and others[144] reported the case of a man who suffered an attack of tonsillitis for which he was given Dicrysticin (penicillin and streptomycin) intramuscularly and also sulfathiazole by mouth. Six days later, he had a constricted feeling in the chest, pain in the ankles, frequency, nocturia, headache, fever, and slight swelling of the left forearm; two painful nodules appeared on the flexor and dorsal surfaces of the left forearm. Biopsy of one of the nodules revealed allergic vasculitis typical of polyarteritis nodosa. Response to cortisone was dramatic. The patient's serum and Dicrysticin were transferred to a volunteer. A nodule was produced which showed the pathologic characteristics of allergic vasculitis. The patient's serum with a suspension of cells from the buffy coat of his blood plus penicillin G showed a lesion characteristic of allergic vasculitis when transferred.

Goncalves[96] presented a review of seventy-eight cases observed in Brazil of "fixed" drug eruptions. The barbiturates were found to be the most common offenders. Cross reactions between the barbiturates were noted. Sulfonamides were the cause in some cases. Phenolphthalein and aminopyrine, which are common causes of fixed drug eruption in other countries, are rarely causative agents in Brazil. In twelve cases of "fixed" drug eruptions caused by oral or parenteral administration, Goncalves[95] rubbed the previously affected spots with specific ingredients held in a solution of propylene glycol. A positive reaction was obtained in four cases. Tests on uninvolved areas gave negative results. Kerlan[122] has outlined the FDA protection as it concerns the dermatologist. A Pilot Study on Reporting of Adverse Reactions to Drugs has been established. This has been set up in co-operation with a group of allied agencies interested in food and drug problems. It is known that little can be accomplished on the basis of a single adverse report of a drug. However, a series of reports furnish a pattern that would permit evaluation of the product and allow the institution of corrective measures where necessary.

In response to a question on the presence of antibiotics in milk, the consultant[175] stated that the question of the presence of antibiotics in foods has been a serious concern to biological scientists, animal husbandmen, and public health officials. The antibiotics are of value as therapeutic or prophylactic agents and growth stimulants in domestic animals. The great majority of research workers are on record as saying that antibiotics do not constitute a problem to human beings if correctly used. The infusion of the udder of cows with antibiotics is a common treatment for mastitis and is carried out by both veterinarians and lay personnel. Veterinarians usually recommend that milk not be used for human consumption for at least seventy-two hours after the injection of the therapeutic agent. In numerous instances, milk and cheese containing antibiotics have entered the commercial market. Circumstantial evidence suggests that antibiotics in milk could be responsible for some of the allergic reactions that occur in man. A number of milk surveys have been accomplished. An extensive

survey was made of 1,706 samples examined and collected from all of the forty-eight states and the District of Columbia. This survey showed penicillin in concentrations of 0.003 to 0.550 units per milliliter in 5.9 per cent of the samples tested.

Crissey and others[51] have noticed an increasing incidence of eczematous complications in hospitalized patients under treatment for tuberculosis. The chemotherapeutic agents which were most commonly used were combinations of aminosalicyclic acid, dihydrostreptomycin, and isoniazid. The eruptions took a number of forms: one type resembled nummular eczema; another resembled seborrheic dermatitis and in some patients combinations of these two entities were seen. In some instances, the antituberculotic drugs could be continued if the patient were given routine dermatologic management. The seborrheic reactions did not respond to suspensions of selenium disulfide or sodium sulfacetamide. In some cases in which it was essential that the specific drugs for tuberculosis be continued, it was possible to keep the patients under control with small doses of prednisone in spite of the accompanying exfoliative dermatitis. It was also noted that patients with these eczematous eruptions were easily sensitized to topical preparations. It is particularly important to avoid sulfonamides, penicillin, "caine" derivatives, nitrofurazone compounds and ammoniated mercury.

In response to a query regarding the use of antihistamines in the prevention of serum (anaphylactic) reactions, the consultant[171] stated that antihistamines have been widely used to prevent or lessen anaphylactic reactions that may occur after the administration of blood, antitoxins, penicillin, and contrast mediums employed in diagnostic studies. He quoted a number of important references in this field which concern the use of antihistamines mixed with various agents to prevent reactions. The reviewer notes that although it is common for most workers in this field to add an antihistaminic or to give an antihistaminic before the administration of one of these agents, the results reported would not seem to have any statistical significance. The severity of reactions may be somewhat diminished by the use of an antihistamine or epinephrine added to agents which may commonly produce anaphylactic reactions.

Amodiaquine.—Glick[93] described a patient who died of agranulocytosis after taking one table (200 mg) of amodiaquine daily for eight weeks. The reviewer notes that the antimalarial drugs (Aralen, Plaquenil and related drugs) have been used with comparative safety over many months in chronic discoid lupus erythematosus and solar dermatitis.

Antibiotics.—A nationwide survey of severe reactions to antibiotics was reported by Welch and others.[255] Penicillin was found to produce the greatest number and the most severe reactions in comparison to all antibiotics now used. Anaphylactoid shock was the most frequent penicillin-produced reaction, which resulted in a death rate of about 9 per cent. Most reactions to penicillin followed intramuscular administration. Antibiotics may produce life-threatening reactions consisting of shock, superinfections, severe skin reactions and blood dyscrasias, including purpura and ecchymoses. Minor reactions to antibiotics consist of angioneurotic edema and urticaria. The broad-spectrum antibiotics produce relatively few adverse reactions. In the broad-spectrum group, cases of blood dyscrasia were caused more frequently by chloramphenicol.

Aralen.—Granirer[98] described the case of a fifty-eight-year-old woman treated with chloroquine (Aralen) for rheumatoid arthritis. Exfoliative dermatitis occurred twenty days after the institution of treatment with a single dose of 250 mg of chloroquine daily. The eruption gradually cleared when the drug was discontinued. The patient was given prednisone and Chlor-Trimeton as supportive therapy.

Arsenic.—Concern was shown by the public analyst[81] of Coventry, England, who found sodium arsenite in the skins of five of seven samples of potatoes examined. Potato areas are sprayed with sodium arsenite solution, corresponding to a concentration of 10 pounds of the dry powder per acre. In the Warwickshire area, cattle have died from arsenic poisoning as a result of this practice. Four potato sprayers have been found excreting abnormally large quantities of arsenic, in spite of using protective clothing and taking all precautions. It is important to remember that the sensitization and other delayed reactions to arsenic may not appear for many years.

Ascorbic Acid.—In response to a query regarding a substitute for ascorbic acid and citrus fruits in a patient in whom allergic reactions developed, the consultant[195]noted that allergic reactions to ascorbic acid must be very rare. Furthermore, there is no substitute for ascorbic acid. Allergy to citrus fruits is quite common, however, and occurs especially in children in whom atopic dermatitis develops. Many other fruits contain ascorbic acid and may be used as substitutes for citrus fruits. Fresh tomatoes and vegetables contain ascorbic acid.

Barbiturates.—Zussman[270] reported an acute drug reaction caused by the barbiturate fraction of reducing pills. Phenobarbital was introduced into this country in 1911 and many reports of hypersensitivity have been recorded. Eruptions include the generalized morbilliform or scarlatiniform type, the bullous erythema multiforme, the discrete point-size violaceous macules of the "fixed type," urticaria and the generalized exfoliative dermatitis which may be fatal. A forty-five-year-old woman who was known to be sensitive to phenobarbital for many years was given a "reducing pill" by her family physician with a most severe reaction, resulting in generalized exfoliative dermatitis. A number of common reducing pills containing barbiturates plus amphetamine or other sympathomimetic agents are recorded.

Carbimazole.—Tait[245] reported the case of a sixty-six-year-old man in whom a fatal agranulocytic reaction developed during carbimazole therapy. The patient had mild congestive failure. A urinary tract infection developed and he was treated with carbimazole for eleven weeks before becoming acutely ill. The blood count at that time showed 300 white blood cells, of which only 6 per cent were neutrophils. Despite treatment, including blood transfusions and penicillin, the patient died within three days.

Chloramphenicol.—Shaw and McLean[228] reported seven patients in whom aplastic anemia developed after treatment with chloramphenicol. Six of the patients died and the seventh recovered after more than ninety blood transfusions. Of interest was the fact that the first symptom of a blood disease occurred within five to eight weeks of the termination of a course of chloramphenicol. A latent period of this duration has frequently been

recorded by others in patients with aplasia after chloramphenicol therapy. The authors recommend that the use of chloramphenicol be restricted to the treatment of serious infections when organisms are resistant to other antibiotics and other forms of treatment.

Chlorpromazine.—Further observations on the hypersensitivity to chlorpromazine in hospital workers were recorded by Høvding.[111] Hypersensitivity to chlorpromazine developed only in personnel who handled the drug for injection. Those handlers of the tablet exclusively were apparently never sensitized. Precautions similar to the principles applied to streptomycin were established for all personnel. A typical contact dermatitis to chlorpromazine in ten nurses attending mental patients, one full-time male nurse and a pharmacist was described by Seville.[225] The higher incidence among the women was due to the fact that in the women's wards, the chlorpromazine (Largactil) was crushed between spoons and dissolved in boiling water before administration; crushing was not carried out by the male nurse. Strict "no-touch technique" on the part of all personnel was established to avoid further sensitization. Photosensitivity was established as a contributory factor in causing the dermatitis. Blackley[21] reported eight patients who had been receiving chlorpromazine for an average period of three months. Photosensitivity to the drug subsequently developed. Promazine hydrochloride (Sparine) was administered in a dosage of 100 to 250 mg three times daily. The preparation was well tolerated and the dermatitis did not recur. Hollister[110] reported jaundice in seventeen of 900 patients treated with chlorpromazine. If liver function tests show that the jaundice is of the obstructive type, a diagnosis of chlorpromazine jaundice can be established. Skin tests with chlorpromazine in these cases were not diagnostic. Cross sensitivity could not be demonstrated with promazine and this suggests that other phenothiazine derivatives may be used in the treatment of patients in whom hypersensitivity to chlorpromazine develops.

Congo Red.—The Congo-red test is used by MacCuish[136] as a diagnostic procedure in amyloidosis. A forty-seven-year-old man had previously been submitted to pneumonectomy for carcinoma in 1943, and this was followed by the development of an empyema which did not heal until 1950. This is a common background for the development of amyloidosis. An intravenous injection of 10 ml of 1 per cent Congo red in normal saline solution, freshly prepared from a sealed ampule of the powder, was administered. Within two minutes the patient complained of extreme difficulty in breathing and respiration ceased. It was felt that sensitivity to the azo dye was the most likely cause of death.

Contrast Media.—A severe anaphylactoid reaction[42] associated with cardiovascular collapse followed an intravenous injection of a contrast medium in a thirty-five-year-old Negro man. The patient had been given 30 cc of a contrast medium intravenously for a pyelogram. Within fifteen minutes anaphylactic shock occurred. Pulse and blood pressure declined rapidly. He was given an intravenous infusion of 5 per cent dextrose in water and then given 10 mg of Chlor-Trimeton intravenously, followed immediately by epinephrine by the same route. Improvement began about ten minutes later when the patient began to respond to questions. Vasopressor agents were then used to raise the blood pressure to 100/70. An electrocardiogram showed an irregular irregularity, read as flutter fibrillation associated with a variable heart block. Within twelve hours after the

initial symptoms the patient's condition had returned to normal and he showed normal sinus rhythm within thirty-six hours. It was believed that the cardiac irregularity may have been induced by the intravenous injection of epinephrine.

Fumagillin.—Anderson and Fleck[3] reported two different skin reactions noted during therapy with the amebicide Fumagillin. One is a widespread maculopapular eruption and the other a severe scaling process of the hands and feet. It is suggested that the scaling process is caused by the drug and may become secondarily infected by fungi.

Gold.—McKenna[143] described a lichenoid dermatitis following gold therapy which in the main resembles the lichenoid dermatitis so commonly seen after atabrine ingestion in World War II. The preliminary eczematous stage resembles seborrheic dermatitis. This is followed by bluish pigmented, lichenoid, oval lesions with subsequent hyperpigmentation before the eruption clears.

Iododerma.—Post[167] described a forty-one-year-old man who had had a constant skin eruption on the shoulders, trunk, buttocks, and thighs for twenty years. The lesions consisted of numerous small, follicular pustules. He had been treated with ultraviolet light, x-ray, autogenous vaccines, and many kinds of local measures. For the past four years, he has been taking thyroid extracts. Originally it was decided that this patient had an iodide eruption and the question of parapsoriasis lichenoides was raised. The patient subsequently admitted that he had been taking bromides for several years.

Isoniazid.—Mann[138] described a forty-five-year-old man who was given 12 gm of PAS daily along with streptomycin intramuscularly, 1 gm daily, and isoniazid, 200 mg daily, all in three divided oral doses. After twenty-four days of treatment, the patient showed tightness of the chest on deep breathing and moderate bronchial spasm; the hemogram revealed 30 per cent eosinophils. Symptoms were recalled when the patient was given a single 50 mg tablet of isoniazid the first day and 100 mg the second. Symptoms occurred within thirty-six hours after ingestion of the first tablet.

Lidocaine.—Many physicians and dentists use Xylocaine (lidocaine) because it seldom produces toxic reactions. Fatal reactions, however, have been known to occur. This preparation was developed because of a low index of sensitivity and could be used in patients who previously showed reactions to procaine. Morrisset[151] described a patient who was given 0.8 cc of Xylocaine, 2 per cent, with epinephrine 1:50,000, prior to dental surgery. Death followed within minutes, although previously the patient had received this local anesthetic without any symptoms.

Meprobamate.—In response to a query regarding allergic reactions to meprobamate in a sixty-year-old man, the consultant[174] stated that meprobamate is chemically related to mephenesin, the muscle relaxant. The known side effects of meprobamate are drowsiness and urticaria which may be accompanied by fever, nausea and vomiting. In large doses, the drug may potentiate the effects of alcohol, barbiturates, and antihistamines. Friedman and Marmelzat (1956) reported five cases of skin lesions in the ano-

genital area that were extremely pruritic and chiefly but not solely purpuric in nature. Blood dyscrasias have not been reported. A similar case of meprobamate sensitivity was reported by Monahan[146] in a thirty-five-year-old Caucasian male who had taken one 400 mg tablet of meprobamate followed by a highball containing 1 ounce of ethanol. Soon after this, the patient experienced numbness and tingling of the hands and face. Within two hours an attack of syncope developed and he was found to be cyanotic. This finding was accompanied by urticaria of the abdomen and extremities. Symptoms subsided in twenty-four hours. This case was an exact parallel to that reported by E. Davis (1957).[53] Davis[53] reported two cases in which skin eruptions developed after ingestion of a single tablet of meprobamate. Massive purpura developed in the first patient, who was a dentist, aged thirty-six. An intense erythema developed in the second case. Both patients recovered within a few days after the onset of the eruption.

Nadisan.—Burckhardt and others[34] discussed photoallergic dermatitis caused by Nadisan. This is a sulfanilamide-like drug used in the control of diabetes; it is similar to our preparation orinase. Unlike Nadisan, however, orinase is a methylated product. Irradiated patch test techniques were used in two patients to establish the photoallergic character of the eruption.

Novobiocin.—Bridges and others[25] reported that novobiocin can produce serious reactions in children. Four children who showed pronounced sensitivity reactions to this antibiotic are described. One of these four died. The child had received this antibiotic orally in a dosage of 2 gm every twelve hours for eight days before death. The patient was treated for juvenile rheumatoid arthritis. Autopsy showed acute diffuse hepatic necrosis and generalized lymphoid hyperplasia presumably caused by novobiocin. Hughes[122] reported a seven-month-old infant who was given 125 mg of novobiocin (Albamycin) orally three times daily for four days. Three days after the medication was discontinued fever and a generalized macular eruption developed. In addition, severe edema of the hands, feet and fingers was noted. Injections of hydrocortisone brought about rapid recovery.

Parathion.—Parathion is a pesticidal spray used in fields and orchards which leaves a residue on most crops, according to Quinby and Lemmon.[199] Persons who use the spray and other workers among the trees and vines run the risk of poisoning. It was shown that the patients reported in this communication absorbed the poison by the dermal rather than the respiratory route. Symptoms of systemic poisoning occur apparently before the patients show any signs of dermatitis. Symptoms were relieved by doses of atropine, 1/100 grain (0.6 mg), administered at short intervals.

Penicillin.—Nudelman[157] described his experience during an anaphylactic shock that resulted after he had been given 300,000 units of procaine penicillin intramuscularly. He had been given the same drug one month previously. Three additional cases of anaphylactic shock reaction to penicillin are reported. No fatalities occurred. One of the patients had experienced the same reaction several years previously. The true incidence of penicillin anaphylactic reactions is impossible to obtain. Most cases are not reported and many are not recognized. The typical episode appears from a few seconds to ten to fifteen minutes after an injection. A patient

may complain of paresthesias; nausea and vomiting generally follows, and the patient becomes pale and cyanotic. Blood pressure falls, and breathing becomes labored and shallow. Unconsciousness may supervene, and this may be followed by coma, convulsions and death. Infants who react to penicillin may have become sensitized through the placental circulation or through the mother's milk after birth. A case of acute, fatal anaphylaxis following a penicillin injection in a twenty-year-old man was reported by Keohane.[121] An injection of 800,000 units of Duracillin had been given as a precautionary measure following a submucous resection. Two hours following the injection the patient went into severe shock without loss of consciousness. He was given oxygen by mask, Vasoxl intravenously, Coramine intravenously and an intravenous drip containing 1-norepinephrine in 5 per cent dextrose. Twenty units of ACTH and 100 mg of hydrocortisone were added to the drip. A second drip of 500 cc of dextran was also started and approximately one hour later he was somewhat improved. He was given 0.5 cc injections of 0.5 cc of epinephrine later in the day. During the next twenty-four hours, 10 cc of Levophed in 2000 cc of 5 per cent dextrose, 500 cc of dextran and 1500 cc of plasma were given intravenously. He seemed much improved. An antibiotic was administered. One gram of chloramphenicol intramuscularly, 25 mg of cortisone orally every four hours and 50 mg of Phenergan intramuscularly were ordered twice daily. The patient had been vomiting and he was again maintained on 3000 cc of intravenous fluids on the second day. Approximately forty-two hours after the onset of the acute reaction, cyanosis, signs of acute pulmonary edema and circulatory collapse developed, and he became comatous and died approximately one hour later. All organs except the lungs were normal at autopsy. The bronchi were full of blood-stained frothy liquid and the alveoli were filled with fluid. The picture was that of acute pulmonary edema.

When benemid is combined with penicillin, higher and more prolonged blood concentrations of the therapeutic agent result. Ström[240] reported a high incidence of delayed allergic reactions in patients suffering from scarlet fever when the combined penicillin-probenecid agent was used. Urticaria was seen in six patients, and maculopapular eruptions in fifty-two patients. These eruptions were associated with fever in forty-three of fifty-eight patients and with mucous membrane reactions of the Stevens-Johnson type in twenty-four. This combination should be used with caution, particularly in patients with scarlet fever.

A query was raised in reference to a man who sustained a puncture wound from a rusty nail and received at the same time 300,000 units of penicillin followed in half an hour by 1500 units of tetanus antitoxin. Subsequently (in seven days) urticaria and joint pains developed, and recurred several times. The consultant[177] stated that the serum sickness type of reaction could have been caused by either or both the antitoxin and penicillin injection. Recurrent or persistent urticaria and joint involvement may last for many months as a result of either penicillin or horse serum sensitivity, even as long as nine months. An additional opinion was obtained. Serum neuritis has been reported to develop slowly, and the motor impairment may become detectable as late as three months after the administration of the serum. In response to a query concerning prolonged penicillin sensitivity in a seventy-three-year-old man, the consultant[179] stated that the effects of penicillin sensitization may remain and recur over a prolonged period. Because the patient's condition was poorly controlled by corticotropin, the consultant thought that the medicament could be

switched to the newer oral steroids. Since an exfoliative dermatitis had developed, dermatologic measures in addition to steroids were indicated in this case. The dosage of the steroid would vary, depending upon the dose necessary to control the stage of exfoliation. In response to a query regarding skin tests in suspected penicillin hypersensitivity, one consultant[182] stated that two major types of allergic reactions are caused by the therapeutic use of penicillin. The delayed serum sickness type, occurring several days after therapy, consists of urticaria, angioneurotic edema, arthralgia, and joint pains. In these cases, the skin test is of questionable value. The immediate or anaphylactic type of reaction occurs within minutes or an hour or two after the penicillin is administered. This may range from local swelling, urticaria and asthma to shock and death. Such patients give an immediate whealing reaction to penicillin on scratch tests or intradermal tests. In every instance of this type of reaction in twenty patients, all gave a positive immediate reaction. It is possible, however, to have an anaphylactic reaction follow in a patient who has given a negative immediate reaction to penicillin. Recommended skin tests are as follows: scratch test with 5000 units per cubic centimeter; if negative, intradermal injection of 0.01 cc of a solution of 100 units per cubic centimeter; if negative, an intradermal test with 100 units per cubic centimeter may be made. The second consultant recommended as high as 10,000 units per cubic centimeter for final skin testing. The presence of itching or pseudopods is considered a special indication for caution. Maganzini[137] reported the histories of two patients who suffered an anaphylactic reaction following the oral administration of penicillin. A total of thirteen patients are reported in the literature who showed this type of sensitization. The usual precautions concerning skin tests, a careful history, and observation of the patient are described.

Betetto and Graziani[20] studied the cutaneous reactions in a series of 150 patients who were being treated with penicillin. Intradermal tests were made with a solution containing 1000 units of crystalline penicillin G per cubic centimeter. Controls of saline solution were also used. Thirteen per cent of the patients were found to be sensitive to penicillin. Negative results to the intradermal test were reported in the remaining 130 patients, sixty-eight of whom had never been treated with penicillin. The authors believe that intradermal tests should be given before subjecting patients to treatment with antibiotics. In response to a query concerning the possibility of desensitizing persons to penicillin, the consultant[176] replied that no practical reliable method exists for desensitizing penicillin-sensitive patients. This procedure is not without danger in patients anaphylactically or atopically sensitive to penicillin. Use of another antibiotic was suggested. Another consultant stated that desensitization to penicillin has been reported following the use of various techniques. In a patient requiring penicillin for syphilis, for example, urticaria may develop early in the treatment. Hives, however, may disappear despite the further administration of penicillin in some patients. With the use of antihistaminics and corticosteroids, practically any such patient can be treated with penicillin to a successful completion of his course of therapy. The reviewer notes that this might not be the case in patients with a background of asthma or other forms of clinical atopy.

Minno and Davis[154] gave penicillinase in doses of 1 million units in 2 cc of sterile distilled water to patients who had suffered delayed allergic reactions to either procaine or benzathine penicillin. Intravenous administration of penicillinase was followed in one instance by a severe shaking

chill with high temperature, nausea and slight cyanosis requiring epinephrine and steroids for relief. This seems to be an effective preparation in selected cases, however. Zimmerman[268] stated that between 5 and 10 per cent of the unselected population is now allergic to penicillin. The various reactions are described. These include delayed reactions; accelerated and immediate reactions; hyperergic reactions, erythematovesicular, or "Id-like" eruptions, and contact, eczematous dermatitis. Penicillinase is a protein enzyme secreted by Cereus, E. coli and many strains of staphylococci, which destroys penicillin, converting it into nonantigenic and nonantibiotic penicilloic acid. Penicillinase is nontoxic. The effects of an intramuscular injection of one 800,000 unit (2 cc) lasts four to seven days. Response can be expected in from twelve to ninety-six hours in about 80 per cent of cases. If no response occurs after ninety-six hours, a second injection of penicillinase solution should be given. Fewer than 5 per cent of all reported patients have required more than two injections of penicillinase for permanent relief. An occasional patient shows a mild, self-limited, febrile reaction which lasts for a few hours and clears spontaneously after the use of penicillinase.

Phenergan.—Epstein and Rowe[69] presented the case of a fifty-eight-year-old white man who showed photosensitivity to Phenergan and chlorpromazine (Thorazine). Originally contact sensitivity could be demonstrated only to Phenergan, but photocross-sensitivity existed at the same time to chlorpromazine. A discussion of photosensitive, phototoxic and photoallergic mechanisms is presented. Phototoxicity, also called primary photosensitivity, refers to those nonspecific phenomena which can be produced at will in human beings and animals, provided that a sufficient amount of the drug and proper light rays are used. Phototoxic phenomena include the photodynamic reactions in the strict sense, and are characterized by an increased sunburn reaction as seen in the phototoxic reaction from sulfanilamide. Given an adequate dose of this drug injected intradermally and followed by an erythema-producing dose of ultraviolet rays, every person so tested will respond with an increased sunburn reaction at the site of injection. Photoallergic reactions, on the contrary, are not normal, obligatory reactions, and occur only in a small number of individuals. Photoallergic responses, experimentally, appeared only after an incubation period of about ten days. Once an individual had become photoallergic, however, the reaction could be reproduced within twenty-four hours. Sensitivity to Phenergan and chlorpromazine caused both phototoxic and photoallergic reactions. A special feature of photoallergy to phenothiazine derivatives is the fact that many of these patients exhibit a double sensitivity. This consists of a plain contact sensitivity to Phenergan or chlorpromazine itself and a photocontact sensitivity to a presumed oxidation or decomposition product of these drugs formed in the skin. Photocross-sensitivity between Phenergan and chlorpromazine may exist, even though plain contact sensitivity (without light) can be demonstrated only to Phenergan, and vice versa. Photoallergy plays a role only in some cases of photosensitivity to phenothiazine derivatives.

(To be concluded in the March-April issue)

Editorial

The opinions expressed by the writers of editorials in the ANNALS *do not necessarily represent the group opinion of the Board or of the College.*

THE "HOMOLOGOUS DISEASE" OF TRANSPLANTATION

In a recent issue of this journal, immunological tolerance was discussed. At periods before immunological maturity is reached or when the immune response has been abolished by irradiation, the injection with heterologous tissue may render an animal tolerant to subsequent skin grafts from the donor. Further study has shown that this procedure of establishing tolerance is not always innocuous. The transplantation of immunologically active cells of the lymphoid family may lead, in certain genetic situations, to severe damage to the growth and development of the host and sometimes to death. The explanation is that the transplanted tissue once established in the host may produce antibodies against the host's own cellular constituents. Such reactions have been demonstrated not only in the mouse (where they had been observed originally), but also in the rabbit and the rat. The affliction of the host by the antibodies of the transplanted homologous cells has been called homologous or secondary or runt disease (the latter designation from the impairment of growth of the young animals thus affected).

These observations obviously are of great biological interest. They will have to be considered in the attempts of producing tolerance in man for the purpose of organ transplantation and also in the attack upon the problems of replacing bone marrow and lymphoid tissue damaged by irradiation.

More detailed information may be found in the *Annals of the New York Academy of Sciences* (73: No. 3, 1958) which contains the proceedings of the Academy's third Tissue Homotransplantation Conference, particularly the articles by E. R. Billingham (p. 782), J. J. Trentin (p. 799), K. A. Porter *et al.* (p. 819), F. Lee *et al.* (p. 825), M. Simonsen *et al.* (p. 834), and R. H. Egdahl *et al.* (p. 842).

A.J.W.

CONNECTICUT STATE ALLERGY SOCIETY

Officers of the Connecticut State Allergy Society for 1959 are:

President.....Maurice M. Hillman, New Haven
Vice President.....R. Edward Vioni, Bridgeport
Secretary-Treasurer.....Marvin Mogil, New Haven

Papers of Interest

Dunning, M. F.: Jaundice associated with norethandrolone (Nilevar) administration. J.A.M.A., 167:1242 (July 5) 1958.
Transient jaundice occurred in two patients after administration of norethandrolone 1 mg per kg for 14 and 17 weeks. The symptoms were mild, and there were no permanent sequelae.

Schiff, B. L.: Dermatitis from acetazolamide (Diamox). Rhode Island M. J., 41:265 (May), 1958.
Two patients reacted with fixed eruptions, recurring always on the same sites. Related to sulfonamide, acetazolamide must be considered as a possibility in cross sensitization.

Lorenzen, J.: Allergic shock due to penicillin allergy after vaccination against polio. Ugeskr. laeger., 120:319 (Mar. 6), 1958.
Polio vaccine produced by the Danish Statens Seruminstitut contains penicillin, 30 units/dose. In a 46-year-old male patient, injection produced rapid anaphylactic shock, successfully treated with epinephrine.

Taranta, A., Mark, H., Haas, R. C., and Cooper, N. S.: Nodular panniculitis after massive prednisone therapy. Am. J. Med., 25:52 (July), 1958.
After ceasing treatment with large doses of prednisone, nodular panniculitis resembling Weber-Christian syndrome was noted. If looked for, more cases might be found.

Westermann, E.: The effect of 5-hydroxytryptamine (serotonin) on respiration. Arch. exper. Path. u. Pharmakol., 233:518 (June 3) 1958.
The use of experimental animals as dogs, cats, guinea pigs and rats demonstrate different sites of action with varying dosages.

Jackson, G. G., Dowling, H. F., and Anderson, T. O.: Neutralization of common cold agents in volunteers by pooled human globulin. Science, 128:27 (July 4), 1958.
Human gamma globulin contains protective antibodies against the common cold.

Warren, F. O.: Treatment of allergic response to penicillin. Preliminary report. J.A.M.A., 167:708 (June 7) 1958.
Potassium salicylate, (300 mg), sodium p-aminobenzoate, (300 mg) and ascorbic acid (50 mg in tablet form, given four times daily within 24-48 hours completely relieved allergic symptoms in 9 out of 10 patients. ?Rationale.

Rosen, S. H., Castleman, B., and Leibow, A. A.: Pulmonary alveolar proteinosis. New England J. Med., 258:23 (June 5) 1958.
A chronic disease of the lungs with a characteristic histologic pattern, but variable clinical course. is described on the basis of the study of 27 patients. The lesion consists of the deposition within the lumens of the distal air spaces of a PAS-positive granular and floccular proteinaceous material, rich in lipids. Clinically the disease is usually manifested by dyspnea, often associated with cough, sometimes yellow sputum, increased fatigability and loss of weight.

Ritchie, J. M.: Antibiotics in small doses for the common cold. Lancet, 1:618 (Mar. 22) 1958.
It is suggested that short-term treatment with antibiotic agents can without risk drastically diminish the effects of the common cold.

Knouf, E. G.: The combined use of gamma globulin and chloramphenicol in the treatment of refractory infections. Antibiotics Ann., 1957-58.
Ten patients afflicted with refractory infections were successfully treated with gamma globulin and chloramphenicol. Neither gamma globulin nor the antibiotic alone had effected a clinical cure.

Hyde, A. T., Jr.: Significance of verbalization in the shift of allergic symptoms. North Carolina M. J., 19:152, 1958.
Suggests a possible correlation between the achievement of speech and the shift of symptoms from eczema to asthma.

McLeod, M. M.: The pediatrician and preventive allergy. North Carolina M. J., 19:93, 1958.
"Potentially allergic infants and children should be protected from unnecessary exposure to dietary and environmental allergens particularly during illness and convalescence."

Shanon, J.: Topical treatment of psychosomatic skin reactions. Ohio State M. J., 54:745, 1958.
A soothing cleansing colloidal oatmeal preparation for local use is effective as an adjuvant therapy in psychosomatic skin diseases being treated by a tranquilizer and/or psychotherapy.

Conrad, F. G., and Atwell, R. J.: The incidence of pulmonary fungus disease (1951-1956) at the Ohio Tuberculosis Hospital. Ohio State M. J., 54:5, 1958.
Geotrichum is usually a benign sapophyte frequently found in sputum, gastric and normal stool cultures. Occasionally it may be pathogenic, causing a chronic bronchitis with thick gelatinous sputum and occasional hemoptysis or a severe pulmonary disease simulating tuberculosis with fever, tachycardia and cough.

DeBodo, R. C., and Altszuler, N.: Insulin hypersensitivity and physiological insulin antagonists. Physiol. Rev., 38:389 (July) 1958.
Well worth reading. Documented with 461 references.

Rosenthal, A.: Follow-up study of fatal penicillin reactions. J.A.M.A., 167:1118 (June 28) 1958.
Survey of thirty fatal anaphylactic reactions to penicillin. Legal implications and safety measures are discussed.

Goldberg, L. C.: The cutaneous efficacy of 6-methylprednisolone (Medrol) ointment, Am & CT, 5:372, 1958.
About 90 per cent of the patients with atopic dermatitis not only had an excellent local effect, but stated that it was the best ointment they had used on their skin.

Baum, G. L., and Schwarz, J.: Pulmonary histoplasmosis. New England J. Med., 258:14, (Apr. 3) 1958.
In patients with dyspnea, chronic cough, weakness and weight loss, the presence of this disorder should be suspected.

Nathan, L. A.: Use of glucosamine-potentiated tetracycline in the treatment of upper respiratory infections in children. Arch. Pediat., 75:251 (June) 1958.
Of fifty patients, age six months to fouteen years, thirty-eight were cured; in three, therapeutic effect was not noticeable. Over a period of four days, nine showed no response to treatment. The drug was particularly well tolerated.

Rose, J. C., and Lazaro, E. J.: Pulmonary vascular responses to serotonin and effects of certain serotonin antagonists. Circulation Res., 6:283 (May) 1958.
By means of an ingenious technique permitting drugs to be injected into the pulmonary artery and excluded from the systemic circulation, serotonin was proved to be a potent pulmonary vasoconstricting agent.

Zohn, B.: Prophylaxis in allergy. New York J. Med., 58:1527 (May 1) 1958.
Advocates prophylaxis.

Taylor, W. W.: Some problems of insect allergies. Mississippi Doctor, 35:297 (May) 1958.
Tourniquet, epinephrine, antihistaminic agents, steroids and oxygen.

Untracht, S.: Allergic reactions to vaccines. A critical review of reactions to vaccines used for active immunizations. New York J. Med., 58:1724 (May 15) 1958.
Truly critical review.

Yanof, S. A.: Value of intravenous amobarbital sodium in psychosomatic disorders: an access to psychosomatic management. Neglect of its use in internal medicine. Internat. Rec. Med., 171:263 (May) 1958.
Description of ten years' experience in narcoanalysis and narcotherapy. The author has given 12,154 intravenous injections to 1,532 office patients.

News Items

Executive Committee of the International Association of Allergology, elected at the 3rd International Congress on Allergology in Paris. From left to right: Prof. Jose Cortes of Mexico, member of the committee; Prof. E. Letterer of Germany, 3rd Vice President; (in rear) Dr. J. W. Quarles van Ufford of Holland, member of the committee; (ahead) Prof. C. Jimenez Diaz of Spain, President-elect; Dr. B. N. Halpern of France, President; Dr. M. G. Gutmann of Israel, member of the committee; Dr. Vera Walker of Great Britain, member of the committee; Dr. C. H. Walton of Canada, Secretary-General; Dr. E. Bruun of Denmark, Treasurer, and Prof. S. M. Feinberg of the United States, Ex-President, member of the committee. Absent are Dr. J. M. Qintero Fossas of Cuba, First Vice President, and Dr. O .R. Withers of the United States, second Vice President.

TRANSACTIONS OF THE INTERNATIONAL ASSOCIATION OF ALLERGOLOGY MEETING

Copies of abstracts (and in some cases, the full texts) of papers given at the IAA meeting in Paris are available in book form and may be obtained by sending a check for $15.75 (representing cost and postage) either to the Editor of the ANNALS OF ALLERGY, 75 Bay State Road, Boston, Massachusetts, for forwarding to Paris, or directly to: Editor, *Medicales Flammarion, 22* Rue de Vaugirard, Paris 6, France.

Immediate advantage should be taken of this opportunity to acquire the background and details of the most recent advances in all areas of the field of allergy as presented in encyclopedic form by research workers and clinicians from forty-one countries.

NEW YORK ALLERGY SOCIETY

An the annual business meeting of the New York Allergy Society on November 17, 1958, new officers were elected for 1958-1959 as follows.

President	Dr. Aaron D. Spielman
President-Elect	Dr. S. Senior Sack
Vice-President	Dr. Russell C. Grove
Secretary	Dr. Sheppard Siegal
Treasurer	Dr. Joseph H. Fries
Assistant Secretary-Treasurer	Dr. Murray Dworetzky

BOOK REVIEWS

PRAKTIKUM DER ALLERGISCHEN KRANKHEITEN. (Outline of allergic diseases.) G. A. Rost, D. G. R. Findeisen, and I. Niemand-Andersen. 273 pages, 37 figures. Leipzig (Germany): J. A. Barth Verlag, 1958.

This short textbook is written for the use of physicians in general practice. Its approach can best be characterized by the following quotation by the senior author: "In our opinion—that must once be openly stated—it is altogether doubtful, whether the so-called antigen-antibody reaction will be considered in the future as the centerpiece of the pathomechanism of allergic reaction." Thus the immunobiological concepts of cause and effect, which make the study of allergic diseases a unified subdiscipline of science, are replaced in this book by a watered-down version of vague ideas of the past, like "idiosyncrasy," mixed with equally vague ideas of electrobiology, ionic unbalance, hormonal, and psychological disturbances, et cetera, unavoidably intermingled with immunological data both for antiquated and modern. Thus man is still in "splendid isolation" from other animals, in that he is able to become allergic, but cannot produce anaphylactic reactions, whereas animals produce anaphylaxis but no allergic reactivities. The quantitative approach is singularly lacking. Small wonder, that intradermal tests are considered both uncertain and dangerous. The polypragmacy of therapeutic recommendations is another logical result of the ideas expounded in this book. Characteristically, they are often contradicted in the presentation of clinical cases and the procedures of avoidance and prophylaxis, which form the best part of the text. It will gladly be granted, that the experienced allergist will often be stimulated by concepts which are off the line of his thoughts. But a physician who uses this book as an introduction to the understanding and handling of allergic diseases is likely to emerge bewildered rather than enlightened.

A.J.W.

SENSITIVITY REACTIONS TO DRUGS. A Symposium organized by The Council for International Organizations of Medical Sciences, established under the joint auspices of UNESCO and WHO. Edited by M. L. Rosenheim and R. Moulton. 230 pages. Springfield, Illinois: Charles C Thomas, 1958. Price $7.00.

At Liège, Belgium, during July 1957, the Council for International Organizations of Medical Sciences, established under the joint auspices of UNESCO and WHO, held a symposium devoted to sensitivity reactions to drugs. There were fifteen participants representing Belgium, France, Switzerland, Italy, Great Britain and the United States. With a clinician in the chair, and pharmacologists, chemists, hematologists and immunologists spearheading the discussion, the proceedings, recently published, make interesting reading.

Discombe discussed hemolytic reactions to drugs and Marshall Chalmers the megaloblastic anemia noted in patients receiving anticonvulsant drugs. The subject of thrombocytopenic purpura was brought up to date by Ackroyd and also by Dausset. The subject of Agranulocytosis was given to Moeschlin. Bone Marrow Aplasia due to Chloramphenical and Sensitivity Reactions to Antibiotic Agents were both discussed by Garrod and that due to Resorcin and Metacresol by Schubothe. Hoigué described his turbidity test studies on the sera of patients sensitive to drugs, and Chase his studies on antibodies. The Immunological Character of Humeral Antibodies was Halpern's subject, and the chemical structure of drugs in relation to sensitivity was Davies'. Of special interest was Lecomte's description of Drug Reactions as Linked to Histamine Release, and Rich's review of Tissue Reactions.

The present status of so-called Collagen Diseases and of Arthritis were respectively reviewed by St. C. Symmers and by Meyler. To Serafini was given the topic of General Considerations on the Diagnosis of the Untoward Effects of Drugs.

Moulton and Rosenheim of University College Hospital Medical School, London, edited the papers of the Symposium.

In his introduction, Rosenheim sums up the proceedings by saying, "A symposium such as this will have fulfilled its purpose if it defines how far knowledge extends today and if it points the way along which further investigation may extend that knowledge."

Those who treat reactions due to drugs will need Meyler's book. Those who suspect that they may unwittingly have caused some of the less frequently occurring side reactions will want it.

SIDE EFFECTS OF DRUGS 1958. By L .Meyler, M.D. 194 pages. Amsterdam, New York: The Excerpta Medica Foundation, 1958. Price, $6.25.

The second edition of "Side Effects of Drugs" covers the medical literature of the world for the period 1956-1957. No reference is made to the side effects of drugs noted in the first edition published a year ago, but since a cumulative index has been added, this volume covers both years, with those drugs which were described in detail in the first edition shown in italics in the index of the second. Since synonyms appear in parentheses and drug names are shown with inverted commas, the book is complete as of May, 1958.

The drugs are listed alphabetically, and in groups, as, for example, antihistamines, antiamoebics, anthelminthics, et cetera. With a description of the side effects of many drugs is appended a brief abstract of an important communication or case history concerning it.

Paragraphs regarding the statistics of addiction, when applicable, are included, and also pertinent papers as that by Fox on "Why Some Doctors Take Dope" and Moore and Green's, "Systemic Toxic Reactions to Local Anesthetics." An abstract of Welch's FDA report on "Reactions to Antibiotic Agents" is also included. Quoted is a statement taken from the J.A.M.A. (165:874, 1957): "It is believed that only 1 to 5 per cent of the antibiotics and sulfonamides administered in the U.S.A. are given on proper clinical indications." A case report of a patient responsive by intracutaneous skin test to 0.000005 units of penicillin with associated systemic symptoms is highlighted.

The chapter on side effects occasioned by the use of poliomyelitis vaccine is detailed and complete. Every physician in the practice of allergy will need to know the detailed (twelve pages) discussion given to the immediate and late effects of steroid hormones. Of special interest is the report of the allergic phenomena provoked by ACTH and controlled by corticosteroids.

THE LAWS OF SCIENCE

"A scientific law is not to be thought of as having an independent existence which some scientist is fortunate to stumble on. A scientific law is not a part of nature. It is only a way of comprehending nature . . . the chief object of science is to minimalise mental effort. . . . It is in the nature of science that no scientific law can ever be proved to be right. It can only be shown to be plausible. The laws of science are not immutable. They are only human efforts towards parsimony in the comprehension of nature."—THURSTONE, The Vectors of the Mind.